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# News&Features from NIH

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES   Public Health Service   National Institutes of Health

# News&Features
## from NIH

January 1984

In a clinical trial supported by the National Eye Institute, laser treatment reduced by half the risk of central vision loss in patients with signs of ocular histoplasmosis syndrome (OHS), a condition that affects about 1,500 Americans each year.

Impairment of vision occurs in OHS because abnormal new blood vessels growing under the retina leak fluid and blood into the macula, the area of the retina responsible for sharp, detailed vision. See page 2

An NIADDK-supported scientist has found that 13-cis-retinoic acid was successful in treating adjuvant arthritis when given orally to laboratory rats. Adjuvant arthritis resembles human rheumatoid arthritis in its clinical course.

13-cis-retinoic acid has recently been used to treat a variety of skin diseases, especially severe acne and psoriasis.

These new findings offer hope to researchers that the drug will eventually be useful in treating patients with rheumatoid arthritis. See page 5

One of the largest studies ever done on vasectomy showed that men who have undergone the operation are just as healthy as other men, or even healthier than most men.

Since 1976, researchers studied more than 20,000 men in four U.S. cities under a project headed by NICHD. The investigators looked at a wide range of illnesses, including cardiovascular disease and those conditions that might have immunologic causes. See page 7

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# Laser Treatment May Prevent Blindness for Some Victims of Histoplasmosis

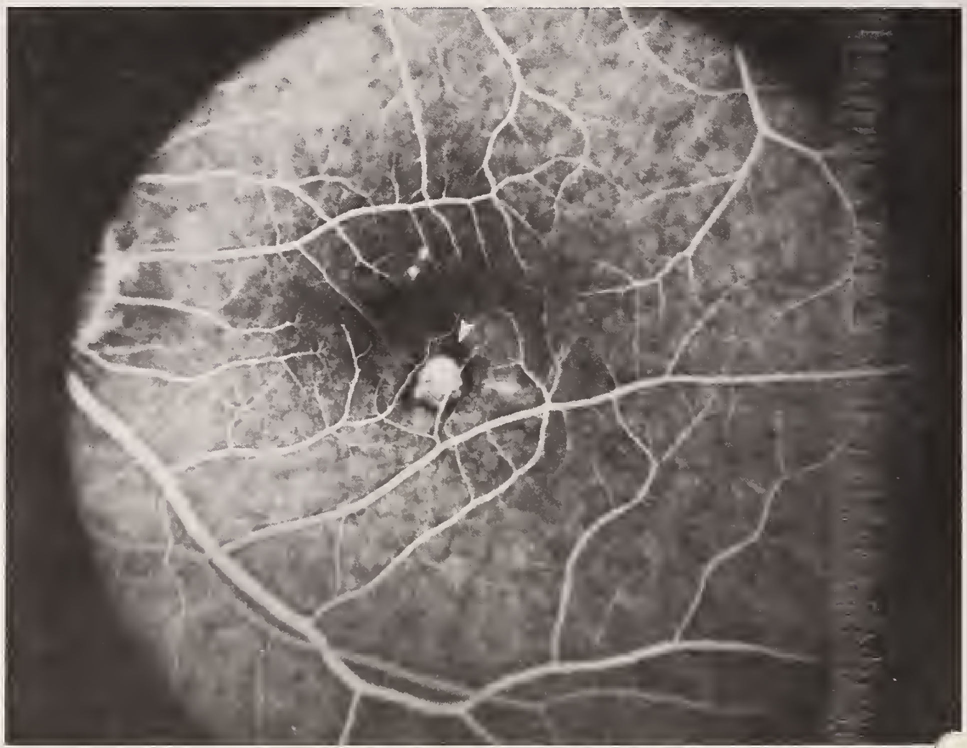
National Eye Institute

The results of a National Eye Institute (NEI)-supported clinical trial demonstrating that laser treatment can prevent serious visual loss in some people with presumed ocular histoplasmosis syndrome (OHS) were recently announced. In this national collaborative study of people who were in danger of losing vision because of OHS, laser treatment cut in half their risk of losing all central vision.

The announcement, made by HHS Secretary Margaret Heckler at a news briefing held at the American Academy of Ophthalmology's annual meeting in Chicago on November 2, pointed out that OHS threatens the vision of some 1500 Americans each year. Sight-threatening OHS is believed to be an unusual and late-developing complication of a common air-borne disease called histoplasmosis. An estimated 20 percent of all Americans and 90 percent of the people in parts of the so-called Histo Belt have been exposed to this disease at some time in their lives. The Histo Belt includes: all of Arkansas, Kentucky, Missouri, Tennessee, and West Virginia; and major portions of Alabama, Illinois, Indiana, Iowa, Kansas, Louisiana, Maryland, Mississippi, Nebraska, Ohio, Oklahoma, Texas, and Virginia.

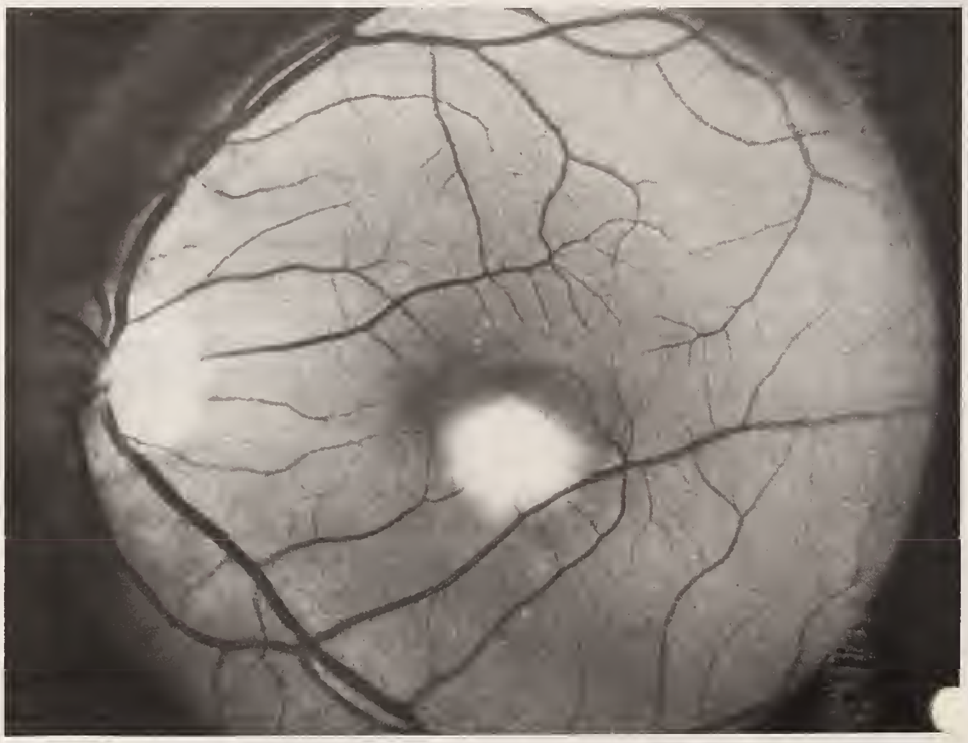
Included in the NEI study were 245 people with clear-cut evidence of OHS. Their visual acuity was impaired because abnormal new blood vessels growing under the retina had leaked fluid and blood into the macula. If unchecked, this leakage can cause irreversible damage to the macula, the area of the retina which is responsible for the sharp, detailed vision needed when reading or driving a car. The goal of argon laser treatment is to stop this process by burning and sealing off the leaking vessels without causing unwanted side-effects.

Participants entering the study agreed to be assigned at random to either the treatment group or the untreated control group. Treatment was usually provided on an outpatient basis in a single visit. People in both groups were examined carefully at regularly scheduled follow-up visits. Information collected during these visits was sent for computer processing and analysis to the study's coordinating center in Baltimore. Statisticians there compiled reports of these data and sent them to an independent group of scientists serving as the Data and Safety Monitoring Committee. The Committee was responsible for deciding when and whether there was evidence of a treatment effect—either positive or



*Arrow points to neovascular membrane where abnormal new blood vessels are growing und the macular portion of the retina of a patient with histo spots (two small white dots).*

NIH Photo 1919



*Twenty-four hours after laser treatment—the neovascular membrane has been sealed off, halting the leakage of fluid and blood which can damage the macula and cause loss of vision.*

NIH Photo 1920

negative—and also if the possible side-effects of treatment were serious enough to outweigh any potential benefits.

To date, more than half of the patients in the 12-center study have been followed for one and a half years, and some for as long as 4 years. In recent months, a significant difference emerged between the untreated and treated eyes. Forty-three percent of the untreated eyes lost most of their central vision within 18 months of entry into the study, while only 19 percent of the eyes which underwent laser treatment experienced such a major loss in visual function. It was therefore concluded that argon laser photocoagulation is effective in reducing the risk of severe visual loss in people with signs of OHS who have abnormal new vessels growing into the macula.

The investigators plan to continue following treated patients for 2 or more years to determine if the observed treatment effect is maintained for longer periods of time. In addition, they are offering to treat people enrolled in the study who were initially assigned to the control group if the condition of their eyes warrants it.

The investigators also have begun to evaluate a newer photocoagulation device, the krypton laser, which may make it feasible to treat more people than is possible with the argon laser. These histo patients have abnormal new vessels that are extremely close to the macula's vital center, the fovea. Until now, investigators have been reluctant to treat these lesions with the argon laser because of the risk of destroying nearby foveal cells that are essential for central vision. There is some evidence that the krypton laser is able to destroy the abnormal vessels and yet spare foveal cells, but this will not be known for sure until the krypton study is completed.

Exposure to histoplasmosis is probably related to contact with, or inhalation of dust from, buildings containing bird, chicken, or bat droppings. The vast majority of people who develop it require little or no treatment to recover from the usually mild, cold- or flu-like lung infection. In fact, most people do not even notice or remember any symptoms. However, about 4 percent of infected people develop a few tiny scars or defects in the retina. These so-called histo spots do not affect vision, nor can they be detected by the person who has them. But 5, 10, or 20 years later, about 5 percent of the people in whom histo spots have been observed begin to experience eye problems that follow a certain characteristic pattern and may lead to loss of vision. Although the relationship between histoplasmosis infection and the sequence of events leading to visual impairment has not been established for certain, ophthalmologists presume that histoplasmosis is the culprit, and often refer to OHS as *presumed* ocular histoplasmosis.

The risk of visual loss from OHS—or from any other cause—can be minimized if an eye doctor is consulted whenever a marked change in vision or an eye problem is noticed. People who know they have histo spots should be particularly alert to any decrease or distortion in their vision and should consult an eye specialist immediately. Only an ophthalmologist who has examined the eyes of a person with symptoms of OHS, and reviewed his or her medical history, can determine whether laser treatment is indicated. Unfortunately, people who have already been blinded by OHS cannot be helped by laser treatment.

A scientific report of the ocular histoplasmosis study appeared in a recent issue of the *Archives of Ophthalmology*. ■

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# Major Depressions and Repeated Hospitalizations Characterize Suicidal Schizophrenics

Judy Folkenberg

Evidence continues to mount on the relationship between depression and suicide.

In a study on suicide attempts by chronic schizophrenics, Dr. Alec Roy, Visiting Associate at the National Institute of Mental Health (NIMH), reports that a greater number of schizophrenics who attempt suicide have experienced a major depressive episode, have received antidepressant medication, and have had significantly more psychiatric admissions than schizophrenics who never attempt suicide.

These new findings join a growing body of information explicating the link between depression and suicide. According to a recent editorial in the *New England Journal of Medicine*, an estimated one out of every six people with major depression eventually kills himself or herself.

Ten percent of the schizophrenic population also commits suicide, and depression may be a major factor, says Roy.

His study examined 127 chronic schizophrenic inpatients who had attempted suicide by various means, including drug overdose, self-inflicted cuts, and hanging.

These schizophrenics had a mean of 5.4 psychiatric admissions, compared with a mean of 3.6 psychiatric admissions for a group of schizophrenics who did not attempt suicide. Nearly 46 percent of the suicidal patients had a major depressive episode, while only 11 percent of those who did not attempt suicide had had a depressive episode.

These differences may indicate that schizophrenics who attempt suicide have a more severe and relapsing form of the illness, Roy suggests, and are more prone to repeated hospitalizations which disrupt their lives.

In fact, he points out, the average age of the suicidal patients in the study was only 26; at such an early stage of adult life, "the destructive effect of repeated psychiatric admissions on future opportunities for employment and healthy relationships can be readily understood," says Roy.

In a previous study on completed suicides among schizophrenics, Roy found that, while a group of suicide victims had been ill the same length of time as a control group, the suicide victims had had a greater number of hospitalizations.

Although virtually no research exists on the prevention of suicide in schizophrenics, Roy believes that certain possible preventive measures need to be explored. One researcher has found that antidepressants can be used as a prophylactic to help prevent depression in schizophrenics who have suffered from the disorder.

Another approach might be to identify schizophrenic persons at risk—those who have exhibited a severe form of schizophrenia, who have experienced depression, who have no social supports, etc.—and develop a special outpatient program for them. Such a program should encompass a range of services, including frequent contact with a therapist, group therapy or planned social interactions, group living arrangements, rehabilitation programs, and/or antidepressant medication, says Roy. ■

# NIEHS Hosts International Meeting on PCBs

Tom Hawkins

The National Institute of Environmental Health Sciences (NIEHS) hosted one of three conferences held worldwide on the potential effects of polychlorinated biphenyls (PCBs) and related persistent chemicals of the halogenated hydrocarbon family. The conference held at NIEHS in September was sponsored by the Department of Health and Human Services Committee to Coordinate Environmental and Related Programs, chaired by Dr. David P. Rall, director of NIEHS and of the National Toxicology Program within DHHS.

The conference was one of three jointly planned to cover a broad spectrum of research on PCBs. NIEHS scientists have participated in all three conferences. The first was held in Fukuoka, Japan, in April 1983, and the third meeting was held in Helsinki, Finland, one week after the conference in North Carolina. "These conferences collectively have enabled us to focus a broad spectrum of international expertise on the PCB questions," Dr. Rall said. "The conference in North Carolina included sessions on formation, disposal and transformation of PCBs; animal and tissue culture toxicology; and on evidence in cases of human exposure and indicators of toxicity."

*Dr. David Rall, NIEHS director, welcomed attendees to the PCB Conference at Research Triangle Park, North Carolina in September.*

NIH Photo 1921

PCBs, which are extremely stable chemicals and slow to disintegrate, were once widely used as insulating fluid in electrical transformers on power lines and in railroad locomotives. PCBs became of public health concern when accidental human exposure and animal tests suggested that these chemicals may have serious long-term health effects. Illegal dumping situations have further increased the interest in research on health effects. Though production and use is now tightly controlled or banned throughout the industrialized world, PCBs are almost universally present in human fat tissue and in the environment.

The proceedings of all three meetings will be published in the NIEHS journal *Environmental Health Perspectives*, Volume 57, scheduled for publication in summer or fall of 1984. ■

# Animal Model Discovered for Beta Thalassemia

Hugh James Lee

A mutant gene similar to one that causes $\beta$-Thalassemia (Cooley's anemia) in humans was recently discovered in mice by scientists at the National Institute of Environmental Health Sciences (NIEHS) and the Research Triangle Institute (RTI), both in Research Triangle Park, North Carolina.

Investigators in the Laboratory of Genetics (NIEHS) and the Chemistry and Life Sciences Group (RTI) found the thalassemia mutation (designated $Hbb^{th-1}$). The mutation was characterized in collaboration with scientists at the National Heart, Lung, and Blood Institute (NHLBI), and the Oak Ridge National Laboratory, Oak Ridge, Tennessee. A deletion (a missing segment of chromosomal DNA) that occurred naturally was found to be responsible for the thalassemic condition in mice. The mutant strain of mice being maintained in the RTI represents the only available animal model for the disease.

The mutation was discovered during electrophoretic screening of $F_1$ progeny from matings of C57BL/6J and DBA/2J mice purchased from the Jackson Laboratory, Bar Harbor, Maine and propagated at the RTI. Blood samples from 11 of 28 offspring in four litters of mice sired by a single DBA/2J male showed aberrant hemoglobin patterns evidenced by absence of $\beta$-major hemoglobin and increased amounts of $\beta$-minor hemoglobin. These mice were then bred to insure maintenance of the mutant gene.

The mutagenesis program is an ongoing NIEHS activity developed by Institute scientists to screen routinely for natural and chemically-induced gene mutations in mice. Mutations causing various degrees of damage to the animals have been identified. Because similar mutations also occur in humans, the studies with mice provide a way to examine the potential genetic harm humans may encounter from exposure to mutagenic substances in the environment. A contractural agreement between the RTI and the Cellular and Genetic Toxicology Branch of NIEHS' Toxicology Research and Testing Program helps to support the project in which the mutant was discovered.

Scientists recently reported using the drug 5-azacytadine to treat a few patients with thalassemia. An experimental drug, 5-azacytadine reactivates a dormant gene to produce the fetal form of hemoglobin. Significant improvements lasting several weeks were reported in the patients who received the drug. No studies have been done on the long-term effects of 5-azacytadine, and scientists point out that these results are very preliminary.

As Dr. David P. Rall, director of NIEHS, points out, "The new mouse model for $\beta$-thalassemia provides an opportunity for this and various other experimental therapies to be investigated more thoroughly than would otherwise be possible. Furthermore, our mutagenesis program will probably lead to the discovery of additional genetic defects in the future and thus be a continuing resource medical research."

This work was reported in the October 1983 issue of *Cell*. ■

# Drug to Treat Skin Diseases Found Successful in Treatment of Arthritis

Barbara Weldon

13-cis-retinoic acid, a drug recently developed to treat a variety of skin diseases and disorders, may also be useful in the treatment of arthritis, according to an article in the August 19, 1983, issue of *Science*.

Using an animal model of arthritis, Dr. Constance E. Brinckerhoff, working at the Dartmouth-Hitchcock Medical Center in New Hampshire, demonstrated that oral doses of 13-cis-retinoic acid markedly reduced joint inflammation associated with adjuvant arthritis. This work was supported by a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

Adjuvant arthritis, as developed in the laboratory rat, resembles human rheumatoid arthritis. Progressive inflammation of the lining of joints, joint swelling and eventual erosion of cartilage and bone occurs in both diseases. Adjuvant arthritis is induced in animals by injecting adjuvant materials into the skin of the back, tail, food pad, or lymph node. After two weeks, the previously healthy rat develops arthritis in the joints of the extremities. Adjuvant arthritis is widely used as a model to identify and test the usefulness of anti-inflammatory compounds for the treatment of arthritis.

Researchers also studied the effect of 13-cis-retinoic acid on the production of collagenase and prostaglandin $E_2$ ($PGE_2$) by cells taken from the inflamed joints of the rat and placed in tissue culture. They found that cells from rats with adjuvant arthritis treated with the drug had decreased levels of collagenase compared to cells from placebo-treated rats with adjuvant arthritis.

This finding is significant because in rheumatoid arthritis, collagenase and $PGE_2$ are synthesized and secreted in large quantities by rheumatoid synovial cells (cells that line the joint). These two compounds are prime mediators of joint destruction seen in rheumatoid diseases. Until recently, only corticosteroids were known to block the production of collagenase by these cells.

The use of retinoids, which are analogues of Vitamin A, to treat adjuvant arthritis is a new application for these drugs. In recent years, naturally occurring all-trans-retinoic acid and synthetic 13-cis-retinoic acid have been used to treat a variety of disorders such as human and experimental cancers, and certain skin diseases, especially severe acne, ichthyosis, and psoriasis.

Dr. Brinckerhoff said in a recent interview that we do not know how the retinoids act on the synovial cells; "We know what they do but not how they do it." She added, "Our ultimate hope is that 13-cis-retinoic acid or other related retinoids will eventually be helpful in treating rheumatoid arthritis. Our purpose is to develop a strong rationale for treating the human disease." ■

# NIH Commemorates Child Health Day

James Hadley

Risk-taking behavior is normal for adolescents and should be viewed as a necessary stage of human development from childhood to adulthood. This is the conclusion of Dr. Diana Baumrind who gave the first annual lecture on October 3 at NIH commemorating National Child Health Day.

The presentation, entitled "Why Adolescents Take Chances—Why They Do Not: Theory and Research," was sponsored by the National Institute of Child Health and Human Development (NICHD).

A noted investigator in the areas of family relations and adolescent behavior, Dr. Baumrind, a research psychologist at the Institute of Human Development at the University of California at Berkeley, believes that "a trusting parent-child relationship may prevent adolescents from seeking involvement in the more serious forms of risk-taking behavior. Yet," she says, "some parental practices may reduce risk-taking behavior at the cost of retarding normal adolescent development." And in some areas of risk-taking behavior, she said peer pressures may supplant parental values and desires.

*Dr. Diana Baumrind addressed the issue of risk-taking behavior in adolescents in the first annual lecture commemorating National Child Health Day.*

NIH Photo 1922

"It is inappropriate to label adolescent behavior as deviant merely because it fails to conform to adult standards," said Dr. Baumrind. "What is appropriate for adults is not appropriate for infants, toddlers or adolescents." She said diversity is an essential characteristic of any stable system—including societies.

"If we wish to encourage the qualities in our youth that lead to enterprise, excellence, achievement and creative accomplishment, we will not attack their risk-seeking proclivities or nontraditional views. Instead," she said, "we will talk about calculated risk-taking and responsible pleasure-seeking. Intervention efforts with youth should be directed, not against their risk-taking propensities, but against uncontrolled, impulsive irresponsible risk-taking."

Teenagers are just as interested in health issues as adults, said Dr. Baumrind. "Adolescents respond positively to solid information that demonstrates the harmfulness of a given practice when that information is presented clearly and without ambivalence."

For example, she pointed out an anti-smoking campaign directed at high school youth in Berkeley. She said it was successful "because it was founded on hard facts rather than on scare tactics and exaggerated claims."

Dr. Baumrind emphasized the need for similar educational campaigns dealing with drug abuse, teenage pregnancy and venereal disease.

Introducing the lecturer, Dr. Mortimer B. Lipsett, NICHD director, said that selecting adolescent risk-taking as the topic to mark Child Health Day emphasizes the Institute's commitment to promoting the relatively new area of behavioral pediatrics. This field integrates the behavioral and social, as well as the biological determinants of disease and health.

"One example of behavioral pediatrics—adolescent risk-taking behavior—is an area of great importance," says Dr. Lipsett. "Accidents are the leading, single cause of death among young people, followed closely by homicide and suicide. Drug and alcohol abuse and inappropriate sexual behaviors are also problems in this age group."

"In addition," he said, "many health behaviors such as cigarette smoking and eating habits—which have a profound effect on adult health and well-being—have their origins during this period of life. Thus, research that contributes to our understanding of how childhood behavior influences adolescent and adult health behavior patterns will have far-reaching consequences." ■

# New Drug Found to be Effective in Treatment of Uveitis

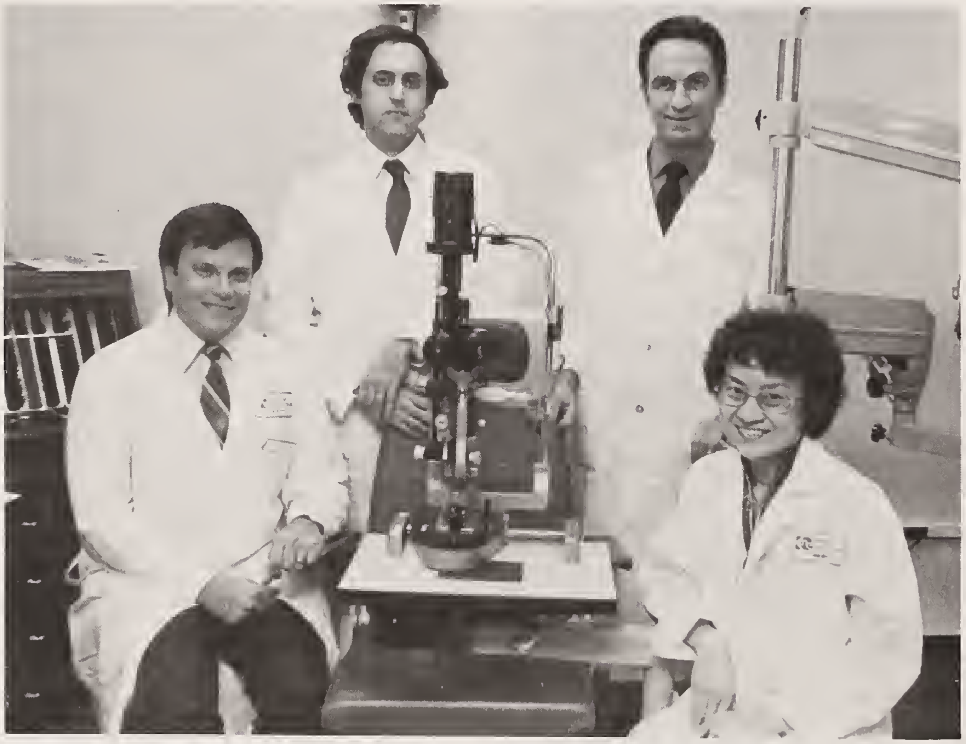
National Eye Institute

People in grave danger of going blind from an eye disease responsible for 10 percent of all visual impairment in the United States have experienced a lasting improvement in vision following use of a new investigational drug called cyclosporine.

The eye disease, uveitis, is responsible for severe visual impairment in an estimated 70,000 Americans, 23,000 of whom are seriously enough affected by this ocular inflammation to be classified as legally blind. In research conducted at the National Eye Institute (NEI), investigators found that people who did not respond previously to standard therapy benefited from cyclosporine. These patients had a form of uveitis which affects tissues at the back of the eye (posterior uveitis). Although the drugs commonly used for posterior uveitis help many patients, they are ineffective or cause harmful side-effects in others.

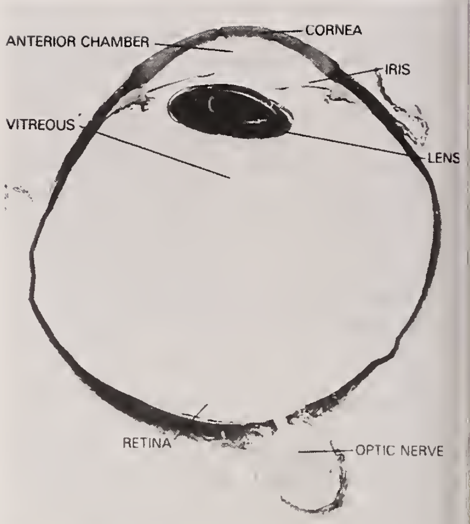
In the recent pilot studies, however, cyclosporine produced such a dramatic improvement in patients with posterior uveitis unresponsive to standard drug therapy that an expanded clinical trial involving up to 300 people has been launched. The trial will be conducted at the National Eye Institute's clinical research facilities on the NIH campus.

People with uveitis who have experienced a reduction in visual acuity and damage to the retina may join the study with their doctor's written recommendation. Physicians interested in referring patients should contact Robert B. Nussenblatt, M.D., Chief of Ophthalmic Immunology, NEI, at (301) 496-1243. The study, which will last for 2 to 3 years, will compare cyclosporine to standard steroid therapy in two similar groups of patients. It is intended to provide more definitive information on whether, and under what circumstances, cyclosporine can improve visual acuity and prevent further visual loss in people with posterior and other types of uveitis.



*National Eye Institute investigators working on cyclosporine treatment for uveitis are (l to r): Drs. Alan Palestine, Clinical Branch; Robert B. Nussenblatt, Clinical Branch; Igal Gery, Laboratory of Vision Research; and Chi-Chao Chan, Clinical Branch.*

NIH Photo 1923



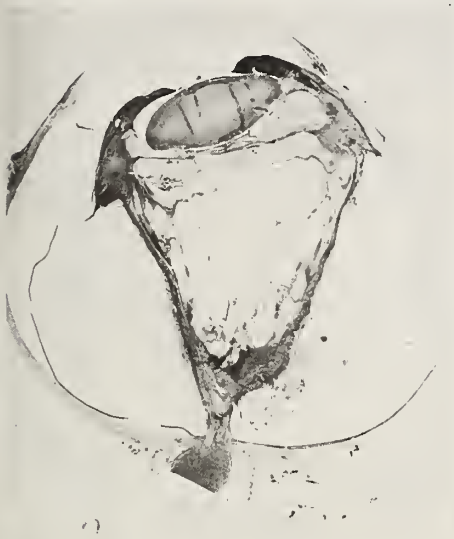
*Cross-section of a normal eye is shown.*

AIH Photo 1924

The study is being conducted by Dr. Nussenblatt and his coworkers, A[illegible] Palestine, M.D., and Chi-Chao Chan, M.D., Clinical Branch, NEI; Igal Gery, Ph.D., Laboratory of Vision Research, NEI; and Alain H. Rook, M.D., National Center for Drugs and Biologics. Dr. Nussenblatt has been studying uveitis for 6 years, both in humans and in an animal model that he and his colleagues developed. From these studies, he began to suspect that at least some of the uveitis patients who do not respond to conventional therapy may have a non-infectious, autoimmune form of the disease in which the body's disease-fighting immune system attacks healthy eye tissues by mistake.

Dr. Nussenblatt selected cyclosporine as a possible treatment for people whose uveitis was suspected to be of the autoimmune type because the drug had already been used with success to prevent rejection of organ transplants by the immune system. His is the first report of cyclosporine being used to treat a human eye disease. The Food and Drug Administration is in the final stages of approving the drug for use in preventing organ transplant rejection but currently classifies it as investigational for ocular disease.

The investigators reported on thei[illegible]search results in a recent issue of *Lancet*. In a pilot study of eight patients with posterior uveitis who had not responded to standard therapy, seven patients experienced a decrease in eye inflammation and disease symptoms, often within 24 hours after the start of cyclosporine therapy. They also showed a measurable improvement in their visual acuity during the first 10 days of treatment. Vision continued to improve in some patients for 6 to 8 weeks after the initiation of cyclosporine. The drug was administered orally; patients were checked every day for 10 days, then every month for up to a year.



*Cross section of eye with uveitis shows extensive damage to tissues of the retina, iris, ciliary body, and the choroid—all tissues of the inner eye.*

NIH Photo 1925

It is believed that cyclosporine impairs the ability of a specific type of white blood cell, the T-cell, to initiate a chain of events that leads to an inflammatory attack on eye tissue. In effect, it prevents white blood cells from triggering a damaging attack on tissue.

Dr. Nussenblatt and his coworkers also developed a blood test that might help them predict which patients are most likely to respond to treatment with cyclosporine. The test is based on earlier studies of animals with an ocular inflammation that is very similar to uveitis in humans. In these animals, the white blood cells react to S-antigen, a normal component of retinal tissue, in a way that is only seen in animals with uveitis. The cells react to S-antigen as if it were a foreign substance, which suggests that an autoimmune process is responsible for the eye inflammation. When animals showing this reaction responded well to cyclosporine, Dr. Nussenblatt and his colleagues decided to test the drug in human uveitis patients whose white blood cells also reacted to S-antigen. The patients who were selected on the basis of this test were mainly those with posterior uveitis. ■

# Results of Largest Study of Vasectomy Revealed

Maureen Gardner

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Men who have had vasectomies are just as healthy as other men, if not more healthy. This conclusion comes from the largest study ever performed on vasectomy, a project involving more than 20,000 men in four U.S. cities.

Researchers compared the rates of a wide range of health problems in men who were not sterilized with the rates in men who had undergone vasectomy one to 41 years ago. The results of this study, called "The Health Status of American Men," were presented on November 14 at the American Public Health Association meeting in Dallas, Texas.

About 10 million U.S. men have had vasectomies, and about 500,000 more undergo the operation each year. After the procedure, men continue to produce sperm, which their bodies absorb. Several years ago, studies showed that one-half to two-thirds of vasectomized men develop antibodies to sperm, an immune reaction which may persist for 10 years or more.

The National Institute of Child Health and Human Development (NICHD) initiated this project in 1976 to find out whether the immune reaction could lead to any health problems in men with vasectomies. The project looked at a wide range of illnesses, which included cardiovascular disease, a potential risk suggested by animal studies. "It is not only the largest, but also the most comprehensive assessment ever conducted of the possible health consequences of vasectomy," according to Ruth Crozier, the study's project officer at NICHD.

Investigators in four research centers collaborated on the study. The research teams were headed by Dr. Frank Massey, Jr., at the University of California, Los Angeles; Dr. Gerald Bernstein at the University of Southern California in Los Angeles; Dr. Leonard Schuman at the University of Minnesota in Minneapolis; and Dr. William O'Fallon at the Mayo Clinic in Rochester, Minnesota.

The researchers used lists of patients in four cities—Los Angeles CA, Eureka CA, Minneapolis MN, and Rochester MN—to identify 10,590 men who had had vasectomies. Half of the men had undergone the operation eight or more years before the study; more than 2,000 of them had been vasectomized for at least 10 years, and nearly 700 had the operation at least 15 years before the study. The number of men available for researchers to assess the risk of rare conditions diminished soon after the 10-year point, so the conclusions are limited to about 10 years after the operation.

For comparison, the researchers paired each vasectomized man with a nonvasectomized man of about the same age, race, and marital status, and who was living in the same neighborhood as the vasectomized man at the time of his operation. Each man was traced to his current location and interviewed.

The men were questioned on a variety of health problems ranging from skin diseases and diabetes to heart diseases and cancers. Of special interest were 54 diseases or conditions that might have immunologic causes, such as rheumatoid arthritis, as well as potential risks suggested by animal studies, such as hardening of the arteries. The men were also asked about health-related behaviors such as smoking and drinking, diet, physical activity, and checkups.

The researchers double-checked the medical histories of virtually all the men—97 percent gave permission—through physicians and medical records. For those men who had died, the researchers obtained death certificates to learn the cause of death.

Results show that before the sterilized men had their vasectomies, there were no striking differences between them and the nonvasectomized men with whom they were paired. In the years following vasectomy, the only condition that was markedly more common in vasectomized men was local inflammation near the site of the operation. This complication, which was previously known, happens infrequently and is usually short-term, occurring mostly within the first year after vasectomy.

Otherwise, the men with vasectomies had no significantly higher rates of any health problems than other men; the rates were either similar for both groups or lower for the men with vasectomies. This held true for several conditions that had been cited as possible complications of vasectomy, including hardening of the arteries, rheumatoid arthritis, blood clotting disorders, and gout. Vasectomized men had fewer deaths from all causes except accidents and violence, which caused the same number of deaths in men with and without vasectomies. ■

# Researchers Work to Solve Mystery of Fragile X Syndrome

James Hadley

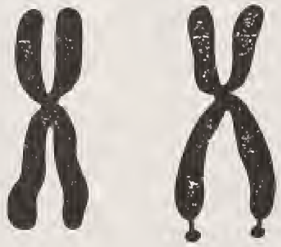
Fragile X syndrome is an elusive genetic abnormality that scientists now think may account for 25 percent of sex-linked mental retardation in men. Its frequency was not recognized until recently.

Of the hundreds of causes of mental retardation, researchers consider fragile X second only to Down syndrome as an identifiable genetic cause of mental retardation in males. Down syndrome occurs about once in every 1,000 births. While estimates vary about the prevalence of fragile X, even conservative figures place its frequency at approximately one in 2,000 males.

Surveys of moderately and severely retarded males in institutions indicate that between 1.5 and 2 percent have the fragile X syndrome. When mildly retarded, non-institutionalized males are included, the estimates of frequency increase even more.

Research is progressing to uncover the mystery of the fragile X syndrome. However, the work is far from complete and the mechanism of its effect remains unknown. Scientists, supported by the National Institute of Child Health and Human Development (NICHD), first discovered the disorder and continue to contribute to the increasing knowledge of the defect.

The name, fragile X, refers to the genetic problem that causes the disorder: a weakening, constriction or defect on the X chromosome. The X chromosome is one of the two sex-determining bundles of genetic material in human cells. Male cells contain one X and one Y, while female cells carry two Xs.



*The X chromosome on the left is normal, while the one on the right, with an appendage, demonstrates one defect that causes the fragile X syndrome. Other problems, such as a weakening, or constriction on the chromosome can also cause the syndrome. There are even cases where the X chromosome looks normal, yet the fragile X syndrome is present.*

NIH Photo 1926

According to Dr. Felix F. de la Cruz, NICHD special assistant for pediatrics, the scientific community showed little interest in the fragile X syndrome in 1969 when Dr. Herbert Lubs, an NICHD-supported geneticist, then with Yale University, identified four men from the same family who had the defect.

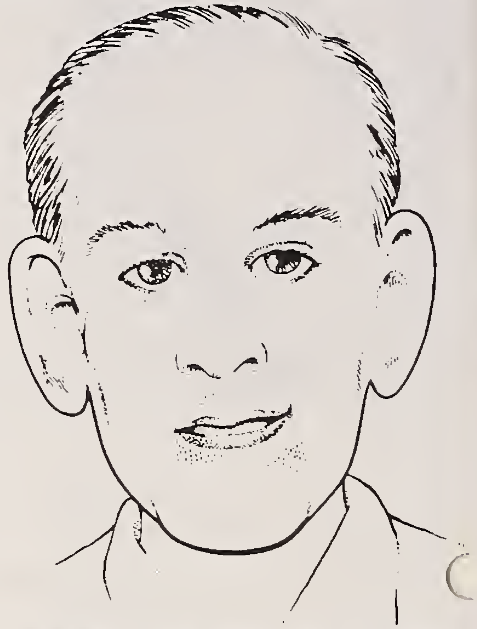
It was almost 10 years later that Australian investigators observed the same syndrome in eight families in which the males had varying degrees of mental retardation.

In research funded by NICHD, scientists later found the fragile X in men from six of the seven families selected for study, thus confirming that the syndrome runs in families. Because of this, physicians now recommend blood tests for chromosomal analysis when couples who want to bear children have a family history of retardation not linked to a known cause—particularly on the father's side.

Dr. Patricia Howard-Peebles, an NICHD-supported researcher, who is director of the Cytogenetics Laboratory and a professor at the University of Texas Health Science Center, says it is important for women under 20 years of age with a family history of mental retardation to be tested to determine if they are carriers of the fragile X chromosome. Women should be tested while they are young because the probability of finding the fragile site on the X chromosome decreases with age.

Although researchers still do not understand the fragile X syndrome, they do agree on its physical signs. They caution, however, that characteristics typical of the syndrome do not guarantee that the fragile X chromosome is present. They also note that generally there are no visible physical signs of fragile X at birth.

Dr. Patricia A. Jacobs, who headed a team of University of Hawaii researchers supported by NICHD, described the general traits in the July 1980 issue of the *American Journal of Medical Genetics*: A variable degree of mental retardation—from mild to severe—but usually moderate; testicles three to four times larger than normal (called macro-orchidism); repetitive speech described as "narrative and compulsive" (for example, "I'm going to the beach, going to the beach."); long facial features with prominent jaw and forehead; and large ears.



*This sketch of a man with the fragile X syndrome depicts the general physical characteristics of the disorder: long facial features with prominent jaw and forehead and large ears. Men may also have increased head circumference. Researchers caution, however, that characteristics typical of the syndrome do not guarantee that the fragile X is present. Although the fragile X syndrome appears predominantly in males, researchers have recently discovered some female carriers who are slightly retarded and may have some of the general traits found in men.*

NIH Photo 1927

Other scientists add that affected males may possess increased head circumference, speech and hearing deficiencies, poor motor control, abnormal behavior and hyperactivity.

Although the fragile X syndrome appears predominantly in males, researchers have recently discovered some female carriers who are slightly retarded and may have some of the general traits found in men. Dr. de la Cruz points out that several studies from different parts of the world, particularly one from Australia, suggest that as many as one third of the female carriers may be mentally retarded to a milder degree than affected males. Sons of a carrier mother have a 50-50 chance of inheriting her fragile X and possessing the syndrome's characteristics.

The syndrome does not appear to be nfined to any ethnic group. It has been und in Caucasians, Blacks, Japanese, Hawaiians, Indonesians, Filipinos and Indians.

"Most investigators believe that the fragile X has no racial predisposition," says Dr. de la Cruz. "The syndrome may be more common in Northern European ethnic groups because of the proportion of affected families seen by different researchers. We simply don't have enough cases to make a comparison. Sampling bias may contribute to this disparity."

Cases are diagnosed by culturing white blood cells until they grow and divide. At this point chromosomes can be analyzed and the fragile X identified.

By accident, a researcher changed his culturing technique and discovered that the fragile X could be detected when the cells were cultured in a solution lacking two agents: folic acid and thymidine.

Dr. Thomas Glover, an NICHD researcher from the Southwest Biomedical Research Institute in Arizona, showed in 1981 that adding a chemical which deters folic acid action increases the probability of identifying fragile X. This discovery greatly enhanced efforts to diagnose the condition before birth.

Recently some researchers reported that fragile X, like Down syndrome, may be detected by extracting amniotic fluid from the womb and testing the fetal cells. More research is planned to improve this testing approach.

A group of international experts concluded at an NICHD workshop on fragile X that more studies are needed in all phases of fragile X research. To help guide the developing body of knowledge, the panel recommended: More research involving family members to help explain why fragile X runs in certain families; guidelines to clearly define the physical and behavioral traits; establishment of DNA and cell banks for future research; application of recombinant DNA methods; more studies on the culturing techniques; and more research aimed at prenatal diagnosis of the condition. ■

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# MEDICAL CAPSULES

Sandra D. Levine

- Scientists have found that children with metastatic neuroblastoma, a nerve tissue cancer that spreads to many organs of the body, have elevated levels of the enzyme neuron-specific enolase (NSE) in their blood.

Partially funded by the National Cancer Institute (NCI), the Children's Cancer Study Group, composed of 29 centers, collaborated on the study under Dr. Paul Zeltzer of the University of Texas Health Science Center at San Antonio, and Dr. Paul Marangos of the National Institute of Mental Health (NIMH) intramural research program. The NSE methodology has been developed over the past eight years by Dr. Marangos at NIMH, and its clinical application is only in its preliminary stages.

Of the 122 children from the U.S and Canada who participated in the study, 96 percent had between 2 and 45 times the normal amount of NSE in their blood.

The level of NSE in the bloodstream predicted which infants would survive. As a prognostic indicator, it can help physicians decide what type of treatment is most appropriate.

Results of this research were published in the August 13 issue of *The Lancet*. Further studies are planned to look at enolase concentration in different tumor stages to determine its accuracy as a marker.

NSE levels are also of diagnostic importance in detecting small cell lung cancer.

- The Second U.S.-Israel Binational Symposium was held at NIH on October 17–19. Keynote speakers included Dr. Baruch Modan, Director-General, Israeli Ministry of Health, and Dr. Edward Brandt, Assistant Secretary, U.S. Department of Health & Human Services.

The Symposium, jointly sponsored by the U.S. Public Health Service and the Israeli Ministry of Health, focused on the contributions of epidemiology to the formulation of health policy. Issues of communicable diseases, chronic diseases, substance abuse and mental health were addressed from such aspects as prevention, assessment of need, resource allocation, and regulatory programs. Proceedings will be published in *Public Health Reports*.

A third symposium, on health policy and technology assessment, is planned for 1985 in Israel.

- The first successful visualization of a neurotransmitter receptor in a living human brain has been achieved by Johns Hopkins scientists. The research was supported by the National Institute of Neurological and Communicative Disorders and Stroke.

The scientists used a positron emission tomography (PET) scanner and a new chemical technique to see dopamine receptors in the parts of the brain involved in motion and emotion. Neurotransmitters such as dopamine are chemicals that send messages from one nerve cell to another. Receptors are small structures on the surface of cells where drugs elicit effects.

The research may lead to a better understanding of Parkinson's disease and other disorders associated with a loss of dopamine receptors.

Using a chemical process called N-alkylation, the scientists attached the radioactive chemical called carbon-11 methyl-iodide to the antischizophrenic drug methyl-spiperone. When methyl-spiperone is injected into the bloodstream, the drug mimics dopamine's ability to bind to the receptor.

Both animals and humans were injected with the radiolabeled methyl-spiperone before examination with a PET scanner. The scanner detected the activity of minute particles called positrons that were emitted by the radioactive label. A computerized reconstruction of the brain then showed where the positrons—and the dopamine receptors—were located.

The new technique, reported in the September 23 issue of *Science*, may also lead to the imaging of other receptors. Visualization of $H_2$ histamine receptors, for example, should provide information about the activity of ulcer drugs. Studying beta-adrenergic receptors should show the action of medications used to treat hypertension and heart disease. In addition, the imaging of opiate receptors in the brain may provide a better understanding of the mechanisms of drug addiction and pain control.

- Researchers at Vanderbilt University Medical Center in Nashville are looking at techniques to reduce the adverse psychological effects experienced by cancer patients undergoing chemotherapy.

The side effects of the anticancer drugs can be so ravaging that anything that even remotely reminds the patients of the chemotherapy can evoke an adverse reaction. Sometimes the aversion becomes so strong that a patient may decide to discontinue treatment.

Under a grant from the National Cancer Institute (NCI), the Vanderbilt researchers are studying muscle relaxation techniques as a possible method of combatting the anxiety-related effects of chemotherapy.

Fifty patients were divided into three groups. One group was taught progressive muscle relaxation and mental visualization of quiet, restful images. The second group was given support by a therapist but received no relaxation training; and the third group received neither training nor support.

Both during and after chemotherapy, the patients trained in relaxation techniques had lower pulse rates and blood pressure, and less anxiety, nausea and vomiting than the others. The only time during which they experienced similar symptoms to those of the controls was in the 12-hour period immediately following administration of the chemotherapy, probably because these are drug-induced reactions.

Used in conjunction with antiemetics and sedatives, self-help strategies such as these muscle relaxation techniques may provide an effective means to help patients cope with the effects of chemotherapy and to give them a sense of control over their symptoms.

**Editors of publications may request a glossy print of the numbered photographs appearing in this issue.**

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# News&Features from NIH

March 1984

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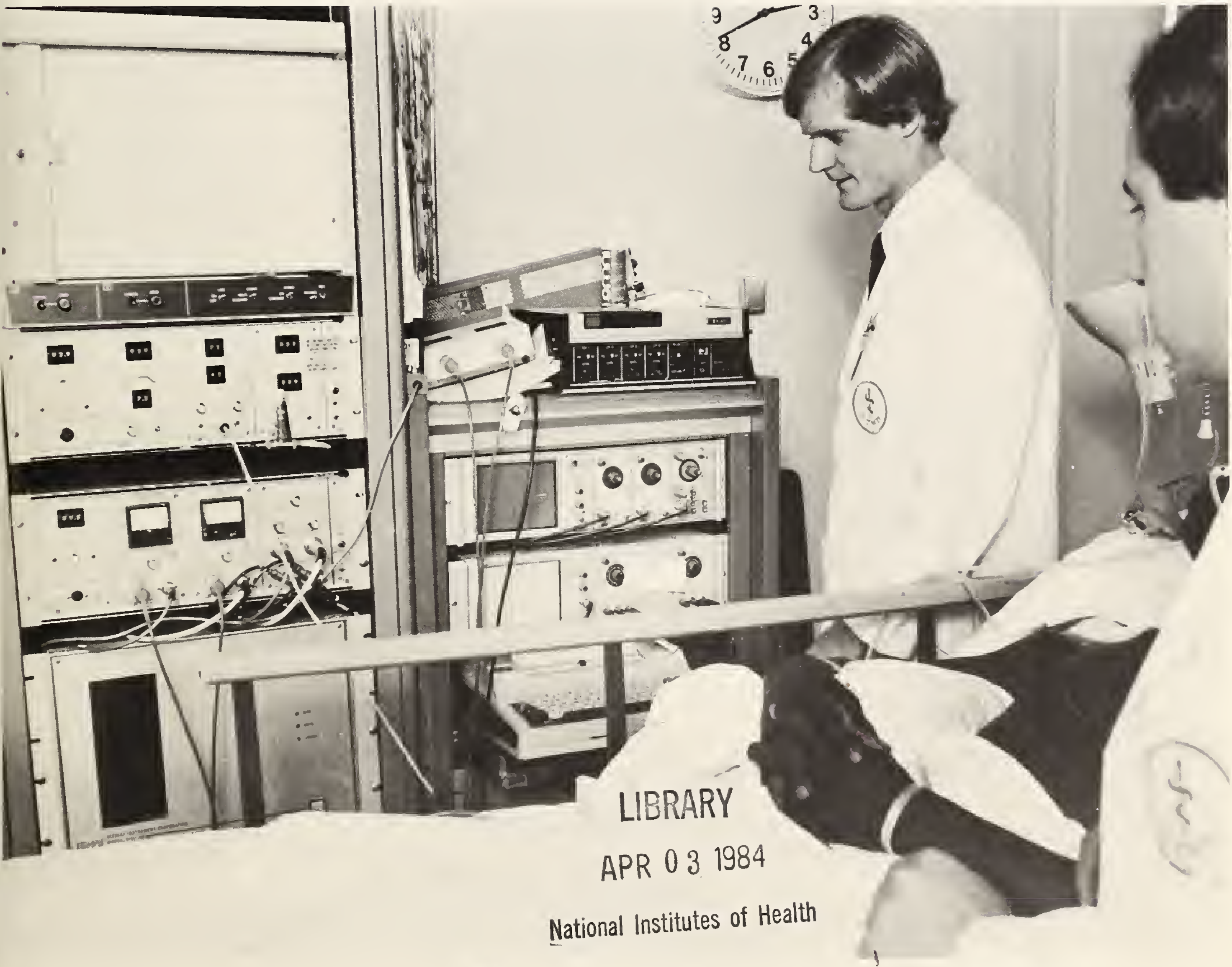
Treatment with Anticancer Drug May Increase Risk of Leukemia **p. 6**

Artificial Chromosome May Lead to Better Understanding of Birth Defects **p. 5**

Tetanus Vaccination of Mother Induces Immunity in the Fetus **p. 6**



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Story on Page 7

**News&Features**
**from NIH**

**March 1984**

**NIH scientists have discovered a genetic marker for Huntington's disease, the illness that afflicted the late folksinger Woody Guthrie. More than 25,000 Americans suffer from Huntington's and another 100,000 live with the risk that the same fate will befall them. Recombinant DNA technology was used to locate the marker, offering hope that gene locations for other inherited illnesses such as cystic fibrosis and Alzheimer's disease may eventually be found. See page 2.**

**Scientists have found for the first time that tetanus vaccine given to a pregnant woman induces immunity in the fetus.**

**NICHD-supported scientist Dr. Thomas Gill studied 42 women vaccinated at the sixth and eighth month of pregnancy and found that the tetanus toxoid crossed the placental barrier, enabling the fetus to make its own antibodies *in utero*. Protection lasted longer than a year after birth. See page 6.**

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**Progress is being made in the diagnosis and treatment of traumatic head injuries.**

**Scientists supported by the Neurology institute are studying techniques to look at changes in brain function after injury. These techniques include CT scanning and monitoring electrical activity to predict prognosis for comatosed patients.**

**Their findings may offer new hope for improved survival rates and quality of life for victims of head injury. See page 7.**

**A study of patients with gastrointestinal cancers who were treated with the anticancer drug methyl-CCNU showed that they had a greatly increased risk of developing leukemia at a later date.**

**According to the National Cancer Institute, 17 of 2,067 patients treated with methyl-CCNU from 1974 to 1980 developed leukemic disorders, including acute nonlymphocytic leukemia (ANL). The study does not suggest that patients currently being treated with methyl-CCNU should avoid or stop its use, but the findings do suggest that it is important to use the drug where the possible benefits exceed the risks. See page 6.**

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# Scientists Find Huntington's Disease Marker: Basic Research Leads to Landmark Discovery

Lynn J. Cave

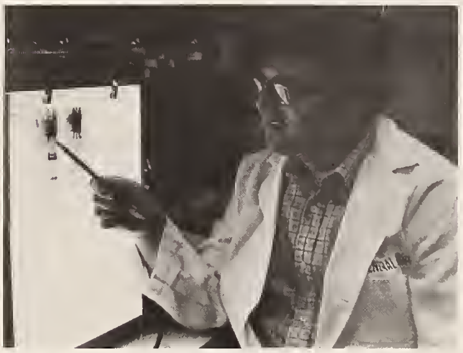
A long-sought genetic marker for Huntington's disease, a fatal nervous system disorder, has been discovered in humans by a scientific team supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the National Institute of General Medical Sciences (NIGMS).

This landmark finding is the critical step in developing a diagnostic test for the disease, according to NINCDS grantee Dr. James F. Gusella, leader of the research team and a member of the Institute-sponsored Huntington's Disease "Center Without Walls" at Massachusetts General Hospital.

"I am optimistic that presymptomatic and prenatal diagnostic procedures will emerge in the near future," he says. Farther down the road, it is hoped the discovery will lead to improved treatments and even a cure for the disease, which causes involuntary movements, emotional disturbance, and intellectual impairment.

More than 25,000 Americans suffer from Huntington's disease, which also afflicted the late folksinger Woody Guthrie. Another 100,000 Americans live with constant dread that the same fate may befall them. Each child of a parent with Huntington's disease stands a 50 percent chance of inheriting the disorder. However, since the illness usually does not appear until age 35 or later, children carrying the defective gene may marry and pass the gene on to the next generation before realizing that they have the disease. Until now, there had been no way to tell, before symptoms appeared, who had inherited the disease gene and who was free of it.

Among Dr. Gusella's collaborators in the gene marker research were Dr. Nancy S. Wexler, a former NINCDS staff member who now heads the Hereditary Disease Foundation, and Dr. P. Michael Conneally, supported by NINCDS and NIGMS, who directs the NINCDS Huntington's Disease Research Roster at Indiana University. The Research Roster, two Huntington's Disease Centers Without Walls, and a research project in Venezuela on the disorder were funded by NINCDS on recommendation of the Congressionally mandated Commission for the Control of Huntington's Disease and Its Consequences, which was convened during the late 1970s.



*NINCDS-supported scientist Dr. James F. Gusella examines a DNA sequence for possible variations that could help locate a Huntington's disease gene.*

NIH Photo 1928

At a press conference to announce the discovery, Dr. Gusella stressed the collaborative nature of the research that for the first time used recombinant DNA technology to find a marker for a gene whose location had eluded investigators for many years. This pioneering venture not only dramatically alters the course for Huntington's disease research, Dr. Gusella said, it also offers hope that gene locations for other inherited illnesses such as cystic fibrosis and familial Alzheimer's disease may now be found.

"The technologies developed to find this marker are transferable to other diseases," says Dr. Wexler, who oversaw the NINCDS Huntington's disease research portfolio until last June. Another candidate disorder for this scientific approach is neurofibromatosis, an illness which involves aberrations of the nervous system.

The discovery of a marker for the Huntington's disease gene was a major goal of Dr. Gusella's project for NINCDS's multi-institutional Centers Without Walls. The achievement, reported in *Nature* in November 1983, was attained with astonishing rapidity in only three years.

To find the marker, Dr. Gusella combined classic principles of genetics with the most advanced recombinant DNA techniques.

Classical genetic studies indicate that if two genes lie close together, they are inherited together. Beginning from this essential premise, Dr. Gusella added new techniques that allowed him to isolate specific sequences of DNA, some of which he hoped would lie close enough to the Huntington's disease gene to be inherited with it and "mark" its presence. But he had no idea which of 46 chromosomes carried the defective gene. Furthermore, the only way to test if a marker was near the Huntington's disease gene was to determine if the marker and the gene "traveled" together through a large family afflicted with the disorder.

"The more people known in the family tree and the more living offspring you have, the greater the power of such a test," Dr. Wexler says.

*Blood and skin samples from hundreds of residents of this stilt village on Venezuela's Lake Maracaibo led the way to the discovery of a genetic marker for Huntington's disease. The residents are descendants of a woman who died of the disease more than a century ago.*

NIH Photo 1929

The needed scientific information came from a U.S. family identified through the Huntington's Disease Research Roster and from a family living in a stilt village built over Lake Maracaibo in Venezuela. The Venezuelan community has one of the highest incidences of Huntington's disease in the world.

An international team of investigators from different institutions in the United States and Venezuela, led by Dr. Wexler, constructed a family tree of more than 3,000 descendants of one Venezuelan woman villager who died of Huntington's disease more than a century ago.

The scientists made several month-long expeditions to the village to perform neurological examinations and collect skin and blood samples from 570 descendants of the woman.

Meanwhile Dr. Gusella was testing his DNA sequences in the American family. His findings suggested that a sequence on chromosome 4 might lie close to the Huntington's disease gene. But the data were not strong enough. He then used the same DNA segment to test the Venezuelan samples, which are currently stored at the NIGMS-supported Human Genetic Mutant Cell Repository in Camden, New Jersey.

Finally, Drs. Gusella and Conneally analyzed the computerized DNA data from the United States and Venezuelan families. The answer was unequivocal. The marker had been found, lying on chromosome 4—extremely close to the Huntington's disease gene.

The diagnostic potential of the Huntington's disease marker is particularly valuable because the disease begins insidiously—with minor clumsiness or forgetfulness. The illness is easily misdiagnosed, which can cause misunderstanding and family problems. For years Woody Guthrie was thought to be an alcoholic until doctors finally determined that he had the disease.

As the disorder progresses, brain cells die. All parts of the body are in constant uncontrollable movement; speech becomes unintelligible, and choking is a hazard. Although intellect deteriorates, insight and orientation often remain. Depression is common and the suicide rate high. Death comes after 10 to 20 years of decline. There are no remissions. Effective treatments do not exist.

Often the illness affects several in a family at the same time. Because the burden of this disease is felt by relatives and friends of the afflicted person, the disorder actually affects hundreds of thousands of lives.

Since each at-risk individual has a fifty-fifty chance of developing the disorder, an early diagnostic test will tell many of those who choose to be screened that the dread for themselves and their children is over. Others, however, probably brothers and sisters of those who escape, will learn that at some time in their future the disease is certain to begin. This makes the need even more urgent to find adequate treatments.

Dr. Gusella cautions that the research team must complete on-going studies before determining the possible worldwide diagnostic application of the marker. He also plans to use a similar approach to find the disease gene itself and to discover the basic defect that gives rise to the illness. However, that will require the development of some new technology.

The recombinant DNA methods used by these investigators should also help scientists who are studying other disorders. "The discovery of the marker is extraordinarily encouraging for anyone concerned with hereditary disease," Dr. Wexler says. "The techniques developed to find the marker have advanced the field so much that other people studying other inherited disorders won't have to start where we started. They'll be ahead of the game."

"With these new techniques," Dr. Gusella adds, "we can aim directly for the gene itself, the ultimate first cause, and try to correct the problem at its root." ■

Before discovering the marker, little was known about Huntington's disease except that its gene is located on an autosome (one of the 44 non-sex chromosomes) and that it is inherited in a dominant manner.

Since knowing a gene's location can aid in identifying it, scientists have long sought to "map" the Huntington's gene by pinpointing its position on one of the chromosomes. One way to do this is to look for other genetic material that willl serve as a marker because it is located close enough to the disease gene that both are inherited together.

The collaborative effort that led to identification of the Huntington's gene marker relied on basic techniques that were developed and refined by scientists supported by the National Institute of General Medical Sciences (NIGMS). Recombinant DNA technology enabled Dr. James F. Gusella of Massachusetts General Hospital and his associates to manipulate DNA from cells taken from Huntington's victims and members of their families by cutting it with enzymes that act only at specific "recognition sites" on the DNA strand. Cutting DNA with these so-called restriction enzymes yields fragments which can then be separated by length. Researchers can see if a particular region of DNA is present in the expected size class by exposing the fragments to a radioactive probe which "sticks" only to the desired DNA fragment.

Scientists using this technique found that the length of particular DNA fragments from different individuals can vary because a recognition site is missing or changed, or because an insertion or deletion of genetic material alters a fragment's size. This has led to the concept of restriction fragment length polymorphism (RFLP).

Several groups of investigators have compared the DNA of individuals afflicted with certain genetic diseases to that of unaffected members of their families. They showed that specific RFLPs are associated with these diseases. Since the gene responsible for a disease may not be known, the associated RFLP can be used as a marker for the disease, as in the case of HD. In addition, regions of DNA near the RFLP can be studied further to try to identify the disease gene.

The contributions of NIGMS grantees to the work of Dr. Gusella and his colleagues go beyond laying the groundwork and providing the basic techniques that made the research possible. The Institute is supporting Dr. P. Michael Conneally, an author of the paper who studied the genetic linkage of Huntington's disease in the family members from whom tissues were obtained for use in this research.

Equally important is the fact that many of these cells were established in culture and stored in the NIGMS Human Genetic Mutant Cell Repository. In cooperation with NINCDS, 3 years ago the cell repository began to accept tissue samples from members of a Venezuelan population that has a high incidence of HD. The repository grew cell lines from these tissues and stored and distributed the cells to interested investigators. Dr. Gusella, one of the collaborators on the Venezuelan project and an NINCDS grantee, used cells from the Venezuelan population to examine a series of restriction fragments of known chromosomal location for association with the Huntington's disease trait. He found a high degree of linkage in a fragment that had previously been shown to reside on chromosome 4. Dr. Gusella and his colleagues were then able to refine the association by screening the cells with a battery of restriction enzymes.

The isolation of a DNA fragment having close association with Huntington's disease is an extremely important research advance. Perhaps as important, though, is that it demonstrates how the techniques of basic molecular biology can be used to attack a disease whose biochemistry is completely unknown and for which there are no known cellular markers.

# NIH-Supported Scientist Wins Lasker Award for Research on Neurobiology

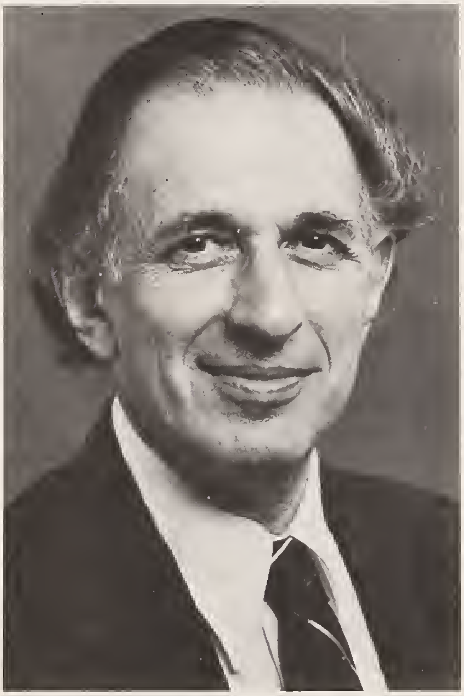
Doris Brody

The Albert Lasker Basic Medical Research Award, often considered a prelude to the Nobel Prize, was recently presented to Eric R. Kandel for his work involving basic research in neurobiology and behavior using the marine snail *Aplysia californica* as a model animal. The award cites him for "remarkably original and systematic investigations of the cellular mechanisms of learning, and for discovering the functional and molecular changes in nerve cells which occur when new information is acquired and stored in memory."

Dr. Kandel is supported by the National Institute of General Medical Sciences (NIGMS), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the National Institute of Mental Health (NIMH).

Dr. Kandel, professor of physiology and psychiatry at Columbia University, shared the $15,000 award with Dr. Vernon Mountcastle of the Johns Hopkins School of Medicine.

In the early 1960's, Dr. Kandel and his colleagues were the first to make intracellular recordings of the firing of individual nerve cells in the hippocampus, the portion of the brain believed to govern memory. The scientists used cats for this research, but sought a simpler animal in which to do studies on the cellular level. They turned to *Aplysia*, a shell-less snail native to the Pacific Ocean and roughly the size of a small squirrel.



*Dr. Eric R. Kandel, an NIH-supported scientist, recently received the Albert Lasker Award for his research in neurobiology.*

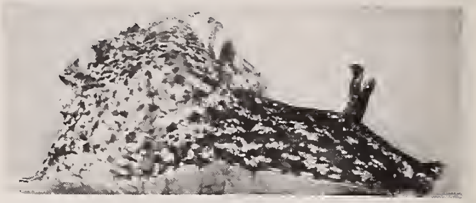
NIH Photo 1930

Because this animal has a relatively simple nervous system and can be conditioned to respond to stimuli in specific ways, it is an ideal creature in which to study physical changes that occur in response to learned behavior. In *Aplysia*, behavior is mediated by only a small number of comparatively large nerve cells and many of these can be identified individually.

Focusing on the snail's gill withdrawal reflex, Dr. Kandel and his associates mapped certain elementary behaviors in *Aplysia* down to the neural circuitry involved. In *Aplysia*, the gill normally lies flat on the animal's back and is bordered by a membrane called the mantle shelf. If this membrane is touched, the gill withdraws into a protective cavity.

The researchers outlined the withdrawal action from the first nerve impulse in the sensory neurons, through intermediary neurons to the motor neurons which activate the withdrawal muscles. Then they began to alter the snail's reflexes through fundamental forms of training and conditioning, and to study changes in cell structure after learning.

In these experiments, Dr. Kandel was able to show for the first time that clear structural changes accompany behavioral modification and that these changes can be detected at the level of identified synapses (junctions where impulses are relayed from one nerve cell to the next via chemical messengers called neurotransmitters) that are critically involved in learning. He showed that learning experiences actually alter the number and size of the sites where neurotransmitters are released to modulate the functional expression of neural connections.



Aplysia Californica, *a shell-less snail from the Pacific Ocean, provided an appropriate model for studying the physical changes that occur in response to learned behavior.*

NIH Photo 1932

The work with *Aplysia* is a very important beginning. However, although nerve cells in *Aplysia* appear to be very similar to human nerve cells, we still know very little about cellular changes related to learning in higher animals and even less about higher mental functions. Eventually, scientists hope to be able to build on this and other fundamental research to gain insight into a range of psychiatric and neurological disorders, as well as those of memory and learning, such as Alzheimer's disease.

In his acceptance speech, Dr. Kandel said, "It will be interesting and exciting to see in the years ahead to what degree higher-order forms of learning, including those that we recognize as unique to ourselves, can be explained in terms of combinations of the simpler components and mechanisms that have been identified in simple animals." ■

# Live, Recombinant Virus Vaccine May Play Key Role in Disease Prevention

Patricia Randall

Almost two hundred years after Edward Jenner's revolutionary discovery of inoculation against smallpox using live vaccinia virus, scientists are using the vaccinia virus to play a key role in another revolution in the field of vaccine production and disease prevention.

Adapting modern techniques of genetic engineering, Dr. Bernard Moss and his colleagues with the National Institute of Allergy and Infectious Diseases (NIAID) are constructing new kinds of recombinant live virus vaccines, made by inserting bits of genetic material from other disease-causing agents into the vaccinia virus. The resulting hybrids retain the vaccinia virus's ability to produce local infection when inoculated in the skin of a wide variety of hosts, thereby stimulating their immune systems.

Drs. Moss and Geoffrey L. Smith have shown that the vaccinia virus can accommodate large amounts of foreign genetic material (*Gene*, November 1983), opening up the possibility that one recombinant live virus vaccine may be able to protect against several diseases at one time.

In December 1983, the NIAID scientists published the first account of a study showing that a recombinant vaccinia virus, containing genetic material from another pathogen, actually can protect susceptible animals (hamsters) against infection by that pathogen—in this case, an influenza virus. This major advance was reported in the *Proceedings of the National Academy of Sciences*.

Earlier work by Drs. Smith, Moss, and Michael Mackett of NIAID showed that a hybrid vaccinia virus containing the gene for hepatitis B virus surface antigen could stimulate antibodies against hepatitis when injected into rabbits. However, since the hepatitis B virus does not naturally infect rabbits, the scientists could not be sure that the antibodies would protect against disease. Studies are underway to test the protectiveness of the recombinant vaccinia-hepatitis virus vaccine in chimpanzees who, like humans, are susceptible to hepatitis B virus infection.

The NIAID team led by Dr. Moss used similar techniques to produce both hybrid vaccinia viruses. Essentially, construction is carried out in two stages. First, the foreign gene is hooked to the specific pieces of vaccinia DNA, or deoxyribonucleic acid, required to make it active, and this modified gene is inserted into an independent segment of genetic material called a plasmid.

In the second stage, the foreign gene is inserted into vaccinia virus by introducing the plasmid into a cell that has been infected with ordinary vaccinia virus. During virus replication in the cell, the modified foreign gene becomes incorporated in genetic material of the vaccinia virus. The resulting hybrid virus can be used as a live virus vaccine to stimulate the immune system of the vaccine recipient.

In the influenza study, animals were inoculated in the skin with the recombinant vaccinia virus. When they were challenged intranasally (through the nose) with influenza virus, the animals had sufficient local immunity in their nasal passages and lungs to prevent respiratory infection. These results suggest that the recombinant virus could be used as a vaccine to prevent infection with influenza or other respiratory viruses in man or other animals.

These recombinant viruses have the potential for being safe, effective, and inexpensive vaccines that can be stored and administered as easily as can smallpox vaccine. Their use would revolutionize disease prevention, particularly in developing countries that cannot afford expensive vaccines and that lack the facilities for complex, multi-injection immunization programs.

Similar work with recombinant vaccinia viruses is also underway at the New York State Department of Health. ■

# First Artificial Chromosome Constructed: Promises New Insight into Birth Defects

Ann Dieffenbach

A team of Harvard medical professors have devised an artificial chromosome that should enable scientists to learn more about how natural chromosomes go awry in such birth defects as Down syndrome.

With support from the National Institute of General Medical Sciences (NIGMS), Drs. Jack W. Szostak and Andrew W. Murray constructed this first artificial chromosome from fragments of yeast and other genetic material and have shown that it performs many of the functions of a normal yeast chromosome.

They chose yeast because it is among the simplest organisms that contain chromosomes structurally similar to those in humans and also because its genetic structure has been well-studied.

Researchers seeking to understand how chromosomes work, until recently, could only do this by studying naturally occurring chromosomes. Now, by using recombinant DNA techniques, scientists can construct and analyze the action of various chromosomal combinations.

Drs. Szostak and Murray began by constructing chains of genetic material containing various combinations of chromosomal elements and comparing their behavior with that of natural yeast chromosomes. This enabled them to identify three regions (in addition to the genes the chromosomes carry) that appear necessary for chromosome function.

The first are origins of replication, sites at which a segment of DNA begins to be copied prior to mitosis (cell division). Next are centromeres, to which the fibers involved in chromosome segregation attach.

Finally, they described telomeres, specialized structures at the ends of chromosomes which play a major role in replication and also keep the ends of chromosomes from sticking together and forming circles. This is important because the chromosomes of higher organisms must be in linear form to function correctly.

These three structural elements were not enough to ensure the proper functioning of the artificial chromosome, however. The researchers found that their synthetic chromosome had to be a certain length—at least one-third as long as the smallest natural yeast chromosome—for it to be stably transmitted in subsequent cell divisions.

The ability of artificially constructed genetic material to be consistently passed on to future generations is an important measure of its similarity to its natural counterpart.

Tests on artificial chromosomes show that they resemble natural chromosomes during mitosis and meiosis (the process which yields sperm or egg cells in humans). However, artificial chromosomes are more likely than natural chromosomes to be lost from one daughter cell during mitosis and, unlike natural chromosomes, may be present in more than one copy per cell. The researchers hypothesize that this reflects the suboptimal behavior of one or more of the functional elements.

Despite these differences, the construction of artificial chromosomes represents a major step toward understanding how chromosomes work.

By making defined changes in artificial chromosomes, it should be possible to discover what features are necessary for normal chromosomal behavior and what mechanisms are involved in such devastating aberrations as Down syndrome. ■

# Fetus Develops Immunity to Tetanus After Mother's Vaccination

Tineke Boddé

Researchers have shown for the first time that a fetus develops its own immunity to tetanus following vaccination of the mother. A research team led by Dr. Thomas J. Gill, III, found that the tetanus vaccine, given to women in the later months of pregnancy, crosses the placenta and enters the fetal blood stream, prompting the fetus to make its own antibodies. The tetanus protection in the child was found to last longer than one year. Dr. Gill, supported by grants from the National Institute of Child Health and Human Development (NICHD), conducted the research at the University of Pittsburgh Medical Center.

According to Delbert H. Dayton, M.D., chief of the Genetics and Teratology Section of NICHD's Center for Research for Mothers and Children, the discovery will benefit families in rural areas of the United States and in developing countries where newborn care is not available or vaccination programs may be difficult to carry out. Dr. Dayton believes that future prenatal immunization may also become possible against streptococcal infections and meningitis.

"It has long been known that a mother's antibodies can cross the placenta," Dr. Gill said. "What we discovered in this study is that the tetanus toxoid can cross the barrier so that the child can make its own antibodies." Parenthetically, Dr. Gill pointed out that he and his colleagues had found in earlier animal studies that immunity in rats can be passed on even into the second generation because the pups' offspring were found to have gained immunity from one single injection to the grandmother.

Three years ago, following extensive experimentation with pregnant rats, Dr. Gill received permission to test the transplacental tetanus immunization on 42 pregnant women. After birth, the infants of these mothers were found to have protection against tetanus in their blood whereas the newborns of 25 unimmunized control mothers did not. The immunized infants also responded more rapidly than the others to DPT immunization (Diphtheria, Pertussis, Tetanus) and they still had a high level of tetanus antibodies 13 months after birth.

Dr. Gill said he chose the tetanus vaccine for his reearch because it is one of the safest, having been used in humans for over 50 years. Women were vaccinated at six and eight months of pregnancy because after five months the major development of the fetal organs has been completed, so that any chance of malformations would be improbable. Dr. Gill said that all infants of the immunized mothers were born healthy and generally remained so during the three-year study.

Dr. Sumner J. Yaffe, director of the NICHD Center for Research for Mothers and Children which monitored Dr. Gill's research, called the successful transplacental immunization highly significant, but warned that further longterm studies on the safety and effectivenss of the vaccination with tetanus and other toxoids were needed before large-scale adoption would be possible.

A report on Dr. Gill's research was published in the September 1983 issue of the *Journal of Clinical Investigation*. ■

# Treatment with Methyl-CCNU for Gastrointestinal Cancers Increases the Risk of Leukemia

Linda Anderson

A followup study of patients with gastrointestinal cancers who were treated with the anticancer drug methyl-CCNU definitively shows that the patients are at increased risk of later developing leukemia. The generic name of the drug is semustine.

Methyl-CCNU is an alkylating agent. The study thus agrees with previous findings that some of the other alkylating agents, a class of drugs effective in treating many forms of cancer, can cause development of leukemia years later. The study is also the first to demonstrate that methyl-CCNU causes leukemia in humans, although some published reports on individual patients have suggested the possibility.

The study, published in the November 3, 1983 issue of *The New England Journal of Medicine*, does not suggest that patients currently being treated with methyl-CCNU should stop or avoid its use since the drug may be useful in treating some cancers. However, the findings do suggest that it is important to use the drug in clinical studies only where the possible benefits exceed the risks. In particular, the findings suggest caution in using the drug for patients at low risk of relapse. In this study, the drug was given as adjuvant therapy to clear the patients' bodies of undetectable cancer cells possibly remaining after complete surgical removal of their cancers. Adjuvant therapy is being used increasingly to attempt to minimize the possibility of recurrence.

The study included 3,633 patients with cancers of the stomach, colon, or rectum, who participated in nine randomized clinical trials of adjuvant therapy. The patients were treated with either surgery alone or surgery followed by various combinations of the following adjuvant treatments: methyl-CCNU, the anticancer drug 5-fluorouracil, radiotherapy, and immunotherapy. The patients began treatment between 1974 and 1980.

Of the 2,067 patients who received methyl-CCNU, 17 later developed leukemic disorders, including nine cases of acute nonlymphocytic leukemia (ANL) and eight cases of preleukemia (bone marrow abnormalities). Preleukemic conditions associated with alkylating agent therapy can be expected to develop into leukemia in one or two years.

Among those who did not receive the drug, only one patient developed ANL. This was not much different from the number that would be expected at the rate in the general U.S. population, 0.6 cases.

Patients who received the drug had a 16-fold increased risk of developing leukemic disorders, compared with patients who did not receive it. No difference in risk was found by sex, age at chemotherapy, or if the patient also had radiotherapy or immunotherapy. Risk was higher among blacks than among whites, but the authors believe that this might represent a chance occurrence.

The study is part of an ongoing assessment by National Cancer Institute (NCI) scientists in collaboration with cancer specialists around the country of long-term treatment effects in cancer patients. The scientists are now conducting analyses of the dose levels of methyl-CCNU, to determine whether risk varied with the dose received by the patients.

All patients who took methyl-CCNU also received 5-fluorouracil. It is possible that the risk for leukemic disorders could have been due to an interaction of the two drugs, but the scientists believe that this is unlikely. When given alone, 5-fluorouracil is not regarded as carcinogenic in humans or laboratory animals, and there were no leukemic complications among those patients who received only 5-fluorouracil. In contrast, methyl-CCNU belongs to a subgroup of alkylating agents called chloroethyl nitrosoureas, which are potent animal carcinogens.

The scientists also looked at data on patients in Connecticut with gastrointestinal cancers who were treated before methyl-CCNU came into use during the mid-1970s. They found no excess of ANL among 44,370 patients who were treated during the years 1935 to 1974. During the latter years of this period, 5-fluorouracil was in use. ■

# Research Improves Prognosis for Head Injury Victims

National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) research program on head trauma promises to improve both the quality of life and the survival rate for head-injury victims. The Institute supports major studies in diagnosis, monitoring, and treatment of head injury.

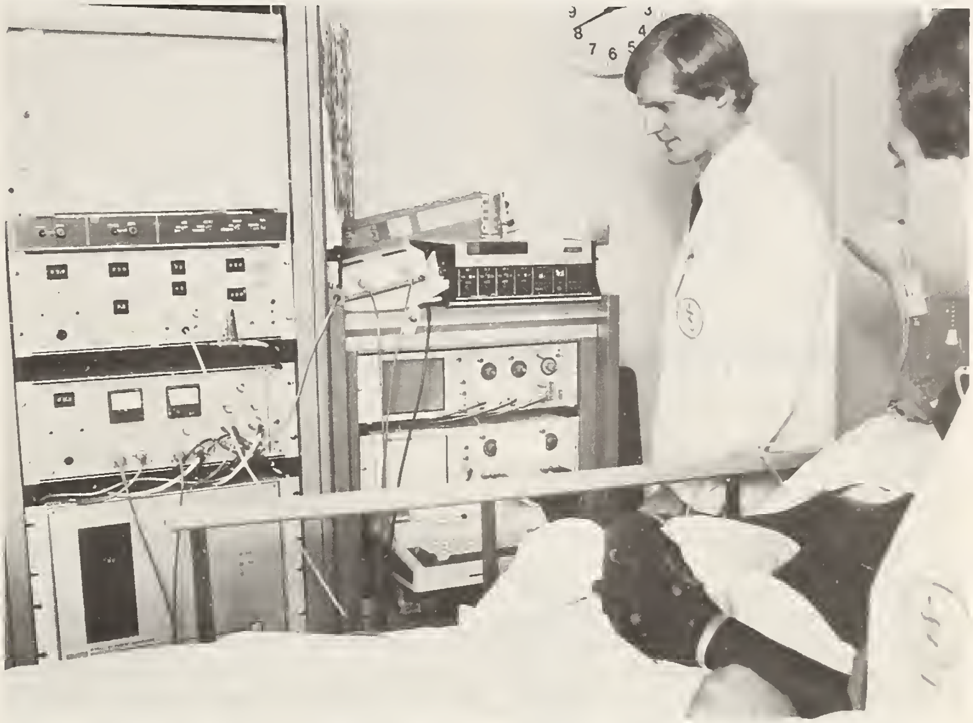
Research conducted by NINCDS-supported scientist Dr. Thomas Langfitt and his group at the University of Pennsylvania in Philadelphia has important implications for the treatment of head injuries. The most common therapy for head injury today is hyperventilation—administration of high levels of oxygen. Dr. Langfitt has found that this form of treatment could be harmful to some patients. Of 75 head injury patients studied, one group had a higher blood flow to the brain than required for the brain's energy needs; other patients, however, had an abnormally low blood flow. Dr. Langfitt concluded that hyperventilation, which constricts blood vessels and reduces the flow of blood and oxygen to the brain, would not be harmful to those patients whose usual brain blood flow was excessive. But, the treatment could be dangerous for patients whose brain blood flow was abnormally low.

In another NINCDS-supported study, Dr. Langfitt and collaborating scientists at the Institute of Neurological Sciences, Glasgow, Scotland, reported significant progress in classifying head injuries—a development that should lead to improved prediction of patient recovery. Using an animal model of head injury, Dr. Langfitt found that 90 percent of the animals studied could be classified as having diffuse axonal injuries—a tearing of axons throughout the white matter of the brain. Axons are fiberlike projections from nerve cells that help transmit chemical "messages" from the brain to the body. Glasgow scientists and NINCDS-supported scientists Drs. Hume Adams and David Graham, collaborating with Dr. Langfitt, further found that diffuse axonal injury in humans could be detected with computerized tomographic (CT) brain scans. Based on both the animal and human studies, the investigators concluded that the severity of diffuse axonal injury determines patient recovery. Evidence of this type of injury on a CT scan, they propose, could be used to forecast a patient's recovery.

CT scanning is also an important part of the research conducted this year by NINCDS-supported scientist Dr. Donald P. Becker of Virginia Commonwealth University, Richmond. He is using CT scans to study devices that monitor pressure on the brain (intracranial pressure). Dr. Becker's research should eliminate unnecessary use of brain-invading devices. The scientist found that patients with normal CT scans should be monitored only if they have two of the following characteristics: age over 40, blood pressure reading less than 90, and abnormal physical movements. Pressure on the brain *should always* be monitored if a patient's CT scan shows any abnormality.

One cause of increased intracranial pressure after head injury is edema—a dangerous collection of fluid within the brain which is triggered by the body's release of several harmful substances. NINCDS-supported scientist Dr. Robert Fishman of the University of California, San Francisco, is examining rat brains in an effort to understand why edema is a delayed reaction—occurring hours or days after head injury. This research may someday lead to an effective treatment for traumatic head injuries in humans.

Another NINCDS-supported scientist Dr. Howard M. Eisenberg of the University of Texas, Galveston, has improved a technique to monitor electrical changes in the brain. He found that certain indicators of the brain's electrical activity can be used to predict whether a person in a coma will improve.



*NINCDS-supported scientists at the University of Texas at Galveston monitor electrical changes in the brain of a head-injured patient. Electrical activity is measured after stimulating the patient's sense of hearing.*

*Photo courtesy of: Div. of Neurosurgery, Dept. of Surgery, The Univ. of Texas Medical Branch at Galveston.*

NIH Photo 1932

Dr. Eisenberg is also studying brain injury in children. It is commonly believed that children with head injuries might have a better rate of recovery than their adult counterparts. However, he found that children with severe brain injury have a slower rate of improvement than adults with similar injuries.

A relatively new brain-imaging technique called positron emission tomography (PET) is helping scientists learn about changes in brain function after injury. The experimental technique, whose development has been funded by NINCDS, is already used in research to identify areas of specific brain function in normal subjects, locate the origins of epileptic seizures, and evaluate brain tumors. Dr. Thomas Langfitt is examining PET scans of head-injured patients in order to learn about the metabolism of specific regions of the brain.

Another brain-imaging technique, called 2-deoxyglucose autoradiography, last year permitted the first study of how specific brain regions in animals function after head injury. This research—conducted by NINCDS-supported scientist

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Dr. Ronald Hayes—may help explain the prolonged loss of consciousness known as coma. Dr. Hayes found decreased brain activity in most areas of the animals' brains, except in one small region where activity was increased. Dr. Hayes speculates that this increased activity may somehow trigger coma-like states in animals, and that a similar increase in activity in a certain part of the human brain may be connected to human coma.

Scientists are improving their ability to predict the outcome of head injuries as a result of information obtained through the NINCDS-sponsored National Traumatic Coma Data Bank. This year, the Traumatic Coma Data Bank was in a transition from pilot to main phase. The goal of the pilot phase was not only to refine data collection techniques for the main study but also to collect detailed information on the factors that influenced the recovery of 581 accident victims. Information was gathered at six head injury centers around the country: University of California, San Diego; Medical College of Virginia, Richmond; University of Texas, Galveston; University of Virginia, Charlottesville; Baylor College of Medicine, Houston, Texas; and Albert Einstein College of Medicine, New York City. Investigators at these centers found that children were more likely than adults to have been injured from falling or from being struck by an automobile. The scientists also reported that children survived their head injuries more often than adults.

The University of California, the University of Texas, and the University of Virginia have been awarded research contracts for the main phase of the Traumatic Coma Data Bank study. Data collected at these center are expected to help scientists determine the factors that influence the survival of head-injury patients and the quality of life survivors can expect. ■

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## Human Monoclonal Antibodies Isolated

Jody Dove

What do diabetes, arthritis, systemic lupus erythematosus, and rheumatic heart disease have in common? These are just a few of many diseases that may involve an immunological "mistake" in which the body is allowed to produce antibodies against itself. Usually, immune responses destroy invading bacteria, viruses, and tumors. However, when misdirected, they may destroy the patient's own tissues.

Although scientists know little about what triggers the production of these autoantibodies, viruses have been suspected as one of the possible causes. Under the direction of Dr. Abner Louis Notkins, chief of the National Institute of Dental Research (NIDR) Laboratory of Oral Medicine, scientists are examining the role of viruses and immunity in human and experimental models of diabetes. Recently, these investigators advanced their exploration through the successful production in culture of mouse and human monoclonal autoantibodies.

The availability of large quantities of these autoantibodies should allow the scientists to identify the antigens these antibodies recognize, the role these antibodies play in autoimmune diseases, and whether different individuals with the same disease develop autoantibodies against the same molecules.

In certain autoimmune diseases, autoantibodies are found that react with a number of organs. One of the difficulties in studying these diseases has been determining whether a variety of autoantibodies actually exist, each reacting with a different organ, or whether the autoimmune response is more restricted, with only a limited number of autoantibodies recognizing common antigens in different organs.

Researchers in the Laboratory of Oral Medicine had previously shown that mice infected with the virus known as reovirus type 1 develop an autoimmune disease of the endocrine glands characterized by mild diabetes mellitus and retarded growth. Autoantibodies against the pancreas, pituitary gland, and mucous-secreting cells of the digestive tract were found in blood samples from these mice. The presence of an immunological component was confirmed when immunosuppression was shown to prevent autoantibody formation, diabetes, and growth retardation.

In order to learn more about the role these autoantibodies actually play, the scientists needed a larger amount of the antibodies than could be isolated from blood samples. Using cell hybridization techniques, Dr. Notkins and his colleagues fused spleen cells from mice with virus-induced autoimmune disease with myeloma cells. Individual hybridomas were cultured, each producing a clone of cells that produced large amounts of identical antibodies.

The scientists were able to generate a large panel of autoantibody-secreting hybridomas, including 14 that reacted with cells in the islets of Langerhans, the insulin-producing part of the pancreas that fails in diabetes mellitus. Twenty-four of the hybridomas made anti-pituitary autoantibodies, 11 made autoantibodies against gastric mucosa, and five made anti-nuclei antibodies. Several of the antigens recognized by these monoclonal antibodies have been identified as hormones, including glucagon, growth hormone, and insulin.

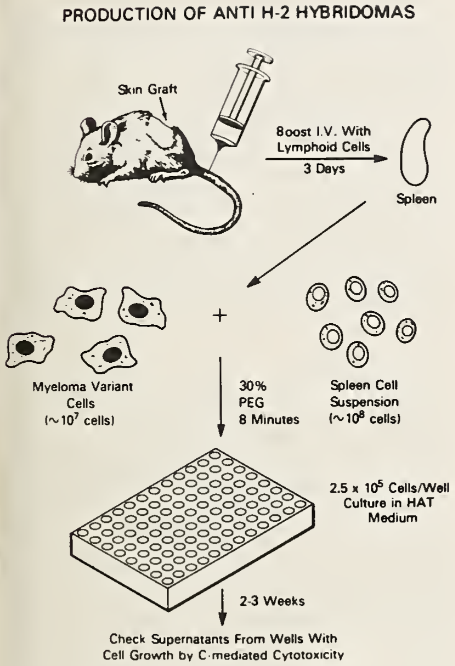
In addition to autoantibodies that react with single organs, the NIDR scientists isolated autoantibody-secreting hybridomas from infected and uninfected animals that reacted with multiple organs. The findings suggest that these monoclonal autoantibodies either recognize the same molecule present in different organs or a common antigenic determinant on different molecules found in multiple organs.

In humans, many children with insulin-dependent diabetes mellitus (IDDM) have autoantibodies in their blood that react with pancreatic islet cells. In some cases, these islet cell antibodies precede the development of IDDM by months, or even years. These antibodies appear to be a useful prognostic indicator for identifying individuals at risk of developing the disease.

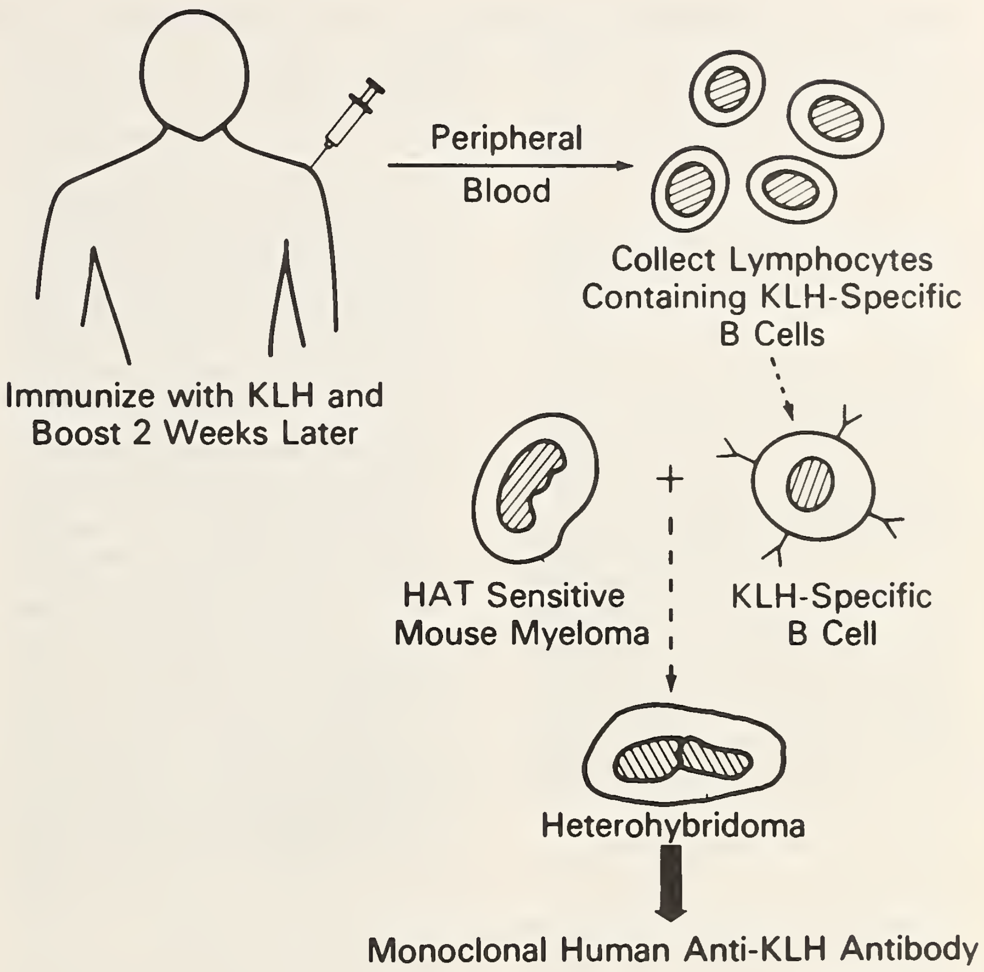
Carrying their research one step further, Dr. Notkins and Drs. Jo Satoh, Bellur S. Prabhakar, Martin V. Haspel, and Fredda Ginsberg-Fellner reported the successful isolation of autoantibodies from humans that react with antigens in multiple organs. Peripheral-blood lymphocytes from patients with insulin-dependent diabetes and other autoimmune abnormalities were fused with either mouse or human myeloma cells. Human monoclonal autoantibodies were obtained that reacted with multiple endocrine (hormone-secreting) and non-endocrine tissues. The NIDR investigators postulate that these antibodies may be a partial explanation for the multiple organ autoimmunity seen in certain autoimmune diseases.

Using these monoclonal antibodies, the scientists are beginning to isolate the specific tissue antigens with which these antibodies react. Thus, these monoclonal antibodies are making it possible to identify some of the autoantigens involved in human autoimmune diseases. ■

# PRODUCTION OF HETEROHYBRIDOMA SECRETING MONOCLONAL HUMAN ANTIBODY OF PREDETERMINED SPECIFICITY


PRODUCTION OF ANTI H-2 HYBRIDOMAS
Skin Graft
Boost I.V. With Lymphoid Cells
3 Days
Spleen
Myeloma Variant Cells (~$10^7$ cells)
+
30% PEG 8 Minutes
Spleen Cell Suspension (~$10^8$ cells)
2.5 x $10^5$ Cells/Well Culture in HAT Medium
2-3 Weeks
Check Supernatants From Wells With Cell Growth by C-mediated Cytotoxicity

NIH Photo 1933


Immunize with KLH and Boost 2 Weeks Later
Peripheral
Blood
Collect Lymphocytes Containing KLH-Specific B Cells
+
HAT Sensitive Mouse Myeloma
KLH-Specific B Cell
Heterohybridoma
Monoclonal Human Anti-KLH Antibody

NIH Photo 1934

*A simple chart illustrates that hybridomas combine the disease-fighting products of the antibody-producing cell with the endlessly dividing qualities of the cancer cell. Among the most recent and noteworthy advances in immunology is the production of monoclonal antibodies from hybrid cells. They are made in the laboratory by fusing an immortal cancer B cell (myeloma) with a normal B cell that produces antibodies. Unlike antibodies produced by immunization, antibodies produced by hybridomas are pure. The antibody-producing cell determines which antibody the hybridoma will make. The myeloma cancer cell gives it the ability to divide repeatedly and grow a harvest of identical antibody in the laboratory. Once fused, each hybridoma becomes a virtually inexhuastible factory, manufacturing large amounts of identical antibody. These antibodies, now available in larger amounts and with greater specificity than ever before, are proving increasingly useful in both medical research and in the diagnosis and treatment of disease.*

*To date, monoclonal antibodies have been used for a variety of biological tasks in the laboratory to accomplish with greater specificity and precision what was done with conventional antibodies before. In the diagnosis of infectious diseases, hybridomas have been used to detect the often subtle differences among populations of viruses and bacteria. Monoclonal antibodies have been used in immunology research to characterize different kinds of T cells—the disease-fighting cells that help both to amplify and suppress antibody production, kill tumor cells and differentiate immature T cells. Because T cells also are responsible for rejecting foreign tissues and organs, immunologists are now intrigued by the possibility of using monoclonal antibodies that are T-cell specific to rid patients' bodies of T-cells before transplants of tissues, such as kidney or bone marrow, are attempted. In the same way, bone marrow might be pretreated to eliminate the cells that are responsible for graft-versus-host disease, in leukemia patients who receive marrow from a donor.*

*In basic cancer research, monoclonal antibodies may help us to understand what distinguishes a cancer cell from a normal cell at the level of the molecule. Monoclonal antibodies are already available that specifically detect the specialized products—enzymes, hormones, and fetal antigens—of certain cancers. Ultimately, monoclonals might help to: detect early cancer, diagnose and discriminate different forms of cancer more finely, monitor the effectiveness of existing cancer treatments (such as chemotherapy or radiation), and treat some cancers.*

*Photos courtesy of: National Cancer Institute, National Institute of Allergy and Infectious Diseases*

# Eye Institute Investigators Work to Reduce Effects of Traumatic Eye Injuries

Mary Lynn Hendrix

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Each year, more than a million Americans experience an eye injury. Forty thousand suffer some degree of visual impairment as a result of their injuries, and 1,500 of those become legally blind.

To reduce the toll of visual loss from eye injuries, the National Eye Institute (NEI) supports research aimed at understanding the response of ocular tissues to trauma and improving the evaluation and treatment of lesions arising from injury.

Among the ocular tissues most susceptible to injury is the cornea, the clear front covering of the eye. This tissue is not only subject to scratches and penetrating wounds from solid objects that come into contact with the eye, but is also vulnerable to chemical and other burns. Currently NEI is supporting studies directed at improving the treatment of alkali burns of the cornea. These burns, which are among the most sight-threatening of all corneal injuries, occur in industrial and agricultural workers who handle phosphates, anhydrous ammonia, and other strongly alkaline chemicals. Other victims of alkali burns receive their eye injuries in domestic disputes in which lye is used as a weapon.

In these corneal injuries caused by alkaline chemicals, there is a high risk that the alkali burn will trigger the release of enzymes that break down collagen, the protein that makes up the basic supporting structure of the cornea. When this happens, large areas of the cornea dissolve leaving a deep ulcer which reaches through the cornea to the inner portion of the eye and exposes it to infection. An eye with a penetrating corneal ulcer of this type will usually have to be removed.

In an effort to develop methods of preventing this disastrous corneal breakdown in alkali burn patients, NEI-supported scientist Roswell Pfister of Brookwood Hospital in Birmingham, Alabama, several years ago began a series of laboratory studies testing two mild organic acids—ascorbic acid (vitamin C) and citric acid—as treatments for alkali burns of the cornea. The results of his studies with rabbits were so promising that an NEI-supported clinical trial was begun under his leadership to test the treatments in patients. Twenty-two medical centers around the country are participating in this trial. The results are expected to give ophthalmologists and hospital emergency room personnel information that will enable them to provide improved care for alkali burns of the eye.

Many NEI-supported studies that were initiated to investigate the normal functions of the eye or ocular disease have turned out to have relevance to the treatment of eye injuries as well. For example, over the past several years Robert Nussenblatt and his colleagues in the NEI Clinical Branch have been studying the mechanisms responsible for uveitis, an inflammatory disease of the inner eye that is responsible for 10 percent of all visual impairment in the United States. They have found that many cases of uveitis are autoimmune in origin. That is, they seem to arise because the body's immune system has mistaken eye tissues for foreign invaders and has mounted an attack against them. This finding was then used to develop a treatment for autoimmune uveitis. The treatment employs cyclosporine, a drug that suppresses certain portions of the immune system. Dr. Nussenblatt's group tested the drug in rats in which autoimmune uveitis had been induced by injection of a protein from the retina (the light-sensing tissue of the eye) into the bloodstream. Preliminary clinical studies employing the drug suggest that it may be an effective treatment in many cases of uveitis.

In the course of these studies, the NEI investigators may also have shed some light on the mechanisms responsible for sympathetic ophthalmia, a rare and little-understood disorder that has long been one of the most dreaded complications of ocular trauma. In sympathetic ophthalmia, a penetrating wound affecting one eye triggers an inflammation resembling uveitis. The inflammation occurs first in the wounded eye and then, perhaps months later, it arises in the other eye as well. If the inflammation is severe, the initial injury in one eye may lead to loss of vision in both.

Although the cause of sympathetic ophthalmia is still unknown, there is every reason to suspect that the disorder may arise through the same mechanisms that are operative in the NEI investigators' rat model of uveitis. That is, the release of retinal proteins into the bloodstream may trigger an autoimmune attack on the eye. If this proves to be the case, there is a possibility that any treatments found to be effective for autoimmune uveitis may also be used to help ocular trauma victims who are in danger of losing the vision of their remaining eye to sympathetic ophthalmia.

Thus the National Eye Institute supports not only research directly aimed at preventing visual loss from ocular trauma, but also a variety of basic and applied studies that can be expected to aid both eye disease and eye injury victims alike.

Fact sheets and brochures on several common eye disorders are available from NEI's Office of Scientific Reporting. ■

# MEDICAL CAPSULES

Sandra D. Levine

• For more than a million Americans hospitalized each year because of kidney and urinary tract stones, NIH-sponsored research offers new hope that recurrence of stones can be prevented.

Investigators have found that treatments using various combinations of drugs and dietary controls prevent recurrence of stones in 72 to 91 percent of patients. Usually about 66 percent of patients can expect a recurrence of the problem after the first incidence of stone formation.

Dr. Charles Y.C. Pak, director of the General Clinical Research Center (GCRC) at the University of Texas Health Science Center in Dallas has found 14 metabolic defects that may lead to renal stone formation. His work at the GCRC is supported by a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). The University of Texas GCRC is one of 75 units funded at medical centers throughout the U.S. by the Division of Research Resources (DRR).

Dr. Pak has found that a new drug, sodium cellulose phosphate (SCP), is effective in controlling "absorptive hypercalciuria." This condition is characterized by excessive absorption of calcium from food, resulting in the formation of calcium kidney stones. SCP, derived from purified wood fiber, binds calcium from food and thereby reduces the amount of calcium absorbed by the body.

In a study of 18 patients treated at the GCRC, Dr. Pak found that after treatment with SCP and a diet restricted in milk products, vitamin C and sodium, kidney stone formation was reduced from almost three kidney stones per year per patient to fewer than one, with no significant side effects.

Further information on the prevention and treatment of kidney stones is available by writing to "Kidney Stones, H/L," NIADDK, Bldg. 31, Room 9A04, Bethesda, Md. 20205.

• Scientists have taken a major step toward replicating tooth enamel, an advance that may create a revolution in restorative dentistry. They hope that the new substance will look better, be more resilient, permit less sensitivity to extremes of temperature, and be more economical than existing restorative materials.

The work to clone tooth enamel is being conducted under a grant from the National Institute of Dental Research (NIDR) by Drs. Malcolm Snead and Harold Slavkin at the University of Southern California in a joint project with Baylor College of Medicine.

They are making considerable progress toward identifying the genetic material that would cause yeast cells to manufacture the protein molecules that form dental enamel. This research into how tooth enamel is formed in the mouse embryo could have far-reaching implications for our understanding of normal and abnormal genetic development in man as well.

• Duke University Medical Center has received a grant from the Biotechnology Resources Program, Division of Research Resources (DRR) to set up a computer model to simulate biomedical systems as a research tool.

Although biomedical simulation is done at several facilities, Duke's Biomedical Simulation Resource will be the first central resource for complex systems that will be available to scientists nationwide, through an extensive data network.

Some of the physiological systems that will be studied include: electrical activity in the muscles and nerves; drug interactions with membranes; and blood clotting mechanisms.

• The healing process appears to be a physiological function that diminishes with age.

According to a study conducted in Philadelphia by Drs. Albert Kligman and Gary Grove, scientists supported by the National Institute on Aging (NIA), the rate of wound healing declines in older patients.

Two groups of subjects, aged 18 to 25 and 65 to 75, were given small, painless blisters on their skin by the application of ammonium hydroxide.

Not only was the healing process slower in the group of older subjects, but the reduced rate of healing corresponded to the lessened rate of new epidermal cell growth, characteristic of the elderly. This finding is consistent with the results of other studies on the effects of the aging process on the skin.

• An experimental drug that may help treat multiple sclerosis (MS) is being tested at Baylor College of Medicine in Houston. The study is funded by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The drug, copolymer, may prevent the destruction of nerve insulation that occurs in patients with MS. This insulating material, called myelin, normally allows the passage of nerve impulses from the brain to the muscles.

Copolymer is being tested at Baylor over a four-year period in 40 patients with the chronic, progressive form of MS. Scientists at Albert Einstein College of Medicine in New York will also test the drug in patients with the intermittent form of the disease.

## A MESSAGE TO SCIENCE WRITERS:
## Arthritis Research Interview Available

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News&Features
from NIH

April 1984

Dental Sealants Can Prevent Tooth Decay **p. 9**

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NIH PHOTO 1935

# News&Features from NIH

April 1984

**A researcher in the Clinical Center's Clinical Pathology Department has designed two non-invasive laboratory tests to aid physicians in early diagnosis of several diseases.**

**One test identifies a particular lipoprotein in the blood that is found in patients who develop angina and heart attacks early in life. Using this procedure, the physician is able to diagnose the problem early, perhaps before an attack occurs, and begin preventive therapy immediately.**

**The second test is used for detecting abnormalities of serum proteins, which can be used as biochemical markers for cancer. Early detection may help physicians intervene therapeutically to minimize or eliminate the threat of disease. See page 10**

**Researchers at NIADDK have been looking at ways to explain the apparent link between liver and brain function.**

**They are testing a new hypothesis that increased levels of gamma-aminobutyric acid (GABA) in the blood may lead to neurological dysfunction. If this should prove to be the case, the development of new drugs may eventually make it possible to counteract the inhibitory brain effects of GABA in coma induced by liver failure. See page 11**

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**Concerns about the safety and effectiveness of the use of ultrasound during pregnancy prompted a Consensus Conference at NIH in February.**

**The Consensus Panel concluded that ultrasound is a beneficial tool to improve the outcome of high-risk pregnancies by helping to identify the cause of problems, or to evaluate fetal growth in pregnancies complicated by disorders such as diabetes and hypertension.**

**The panel, however, concluded that there was not enough evidence as to the benefits of the procedure to endorse routine use of ultrasound screening for pregnant women. See page 5**

An image of the face of a 5-month old fetus appears on an ultrasonogram. (Photo courtesy of News and Publications Service, Stanford University, Stanford, California.) See Story on Page 5.

**An NIH Consensus Panel recently determined that "serious consideration" should be given to withdrawing products containing combinations of some common analgesics from over-the-counter use in the U.S.**

**After two days of testimony, the panel concluded that large doses (a minimum of ten tablets per day over at least a three-day period) of combinations of analgesics such as aspirin, acetaminophen, salicylamide or salicylates, can cause kidney disease and lead to renal failure.**

**Single-agent analgesics, however, were not considered to pose a problem. See page 2**

**Dental sealants offer additional protection against tooth decay, according to a panel of experts at a recent NIH conference. Childen with newly erupted molars are those most likely to benefit from the treatment. See page 9**

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# Serious Consideration of Withdrawing Mixed Analgesics Suggested by NIADDK Consensus Development Panel

James Fordham

"Serious consideration" should be given to the withdrawal of products containing combinations of some common analgesics from over-the-counter use in the United States, according to an NIH Consensus Development Panel. The products involved are those containing mixtures of aspirin, acetaminophen, salicylamide, or salts of salicylates.

Large doses of these antipyretic analgesics taken in combination over a long period cause a specific form of disease (analgesic nephropathy) and can lead to chronic kidney failure, the panel concluded. An example of heavy use would be ten or more tablets per day for three years or longer. The panel estimated the cost of treatment of end-stage renal disease caused by this disorder to be "at least $40 million in the U.S. each year."

The panel also said, however, that: "Preparations containing single antipyretic analgesics such as aspirin or acetaminophen should remain available as over-the-counter medications since there is no evidence that their occasional use is related to analgesic nephropathy. The risk from prolonged use of single-ingredient analgesics appears to be small."

The conference was held February 27–29 and was sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) and the NIH Office of Medical Applications of Research.

The problem of analgesic-associated kidney disease was first reported in the 1950s, and since then has come to be recognized as a significant, costly, and potentially treatable and preventable disease. The condition (described as a chronic tubulo-interstitial nephropathy) is slowly progressive and patients are usually asymptomatic until their kidneys fail. The problem occurs primarily in women who take large doses of analgesic mixtures daily over a period of years. Patients with the disorder often exhibit gastrointestinal disorders, ischemic heart disease, anemia, emotional disturbances, and prematurely aging skin.

Experts estimate that each year more than 250 people in the U.S. develop end-stage kidney disease from overuse of analgesics (about one new case per million population per year). The incidence is much higher in some parts of the nation, however, such as one region of North Carolina, where ten new cases per million occur each year. Moreover, for every patient whose kidneys fail, many other habitual users of painkillers develop milder forms of the disease.

For reasons as yet unknown, the problem is far more common in certain countries outside the U.S., such as Australia, Belgium, Scotland, and Switzerland. In fact, surveys have shown that Australians have an exceedingly high daily consumption of analgesics, and the incidence of the disease in that country has been reported to be "50 times higher than that recorded in the United States and in Europe."

In its consensus statement, the panel noted four clinical and experimental features that are relevant to the pathogenesis of analgesic nephropathy:

(1) The disease is most commonly associated with the ingestion of analgesic mixtures in large doses over a prolonged time.
(2) The initial lesion occurs in the papilla; changes in the cortex are secondary to papillary damage.
(3) Papillary necrosis may be accentuated experimentally and in certain patients by dehydration and low urine volumes.
(4) The major phenacetin metabolite, acetaminophen, as well as salicylates are concentrated in the papilla, particularly during low urine output.

Although the precise pathogenic mechanisms of the disorder are still unclear, the panel concluded that the above features "suggest that the disease results from the effects of a toxic agent or agents in the renal papilla."

The panel stated that: "Present evidence suggests that acetaminophen causes tissue injury as a result of its conversion to toxic metabolites. By lowering the concentration of glutathione, a substance that protects against such tissue injury, aspirin and other salicylates enhance toxicity. Salicylates and acetaminophen also inhibit prostaglandin synthesis and thus may reduce medullary blood flow and potentiate papillary damage."

"These data," according to the panel, "offer attractive though yet unproven explanations for the synergistic effects of phenacetin and aspirin in causing papillary necrosis. They also suggest avenues for research into interactions of other analgesic and anti-inflammatory drugs that may lead to renal disease."

The main strategies in management of cases of analgesic nephropathy suggested by the panel were:

(1) Avoidance of antipyretic-analgesic agents, as well as non-steroidal anti-inflammatory drugs.
(2) Prompt treatment of proven urinary tract infections.
(3) Awareness that a necrotic papilla may slough and obstruct the urinary tract, sometimes requiring prompt intervention to prevent further loss of renal function.
(4) Careful supervision of hypertension.
(5) Recognition that tumors of the urinary tract may occur more frequently in patients with analgesic nephropathy. Unexplained episodes of hematuria, including a marked increase in microscopic hematuria, should therefore be evaluated carefully.

The panel called for more epidemiological research, evaluation of the effectiveness of measures designed to reduce analgesic abuse, research on factors that may predispose patients to the disease, and study of the nature of the toxic metabolites. More research was also recommended on the mechanisms of cell injury in the papilla, the role of ischemic versus toxic factors, and the interactions of drugs in causing papillary damage. In addition, the panel said more information is needed on the relationship between analgesic nephropathy and uroepithelial cancer.

The panel members included nephrologists, pathologists, epidemiologists, pharmacologists, biostatisticians, family physicians, and ethicists. The chairman was Dr. Roscoe R. Robinson, Vice Chancellor for Medical Affairs and Professor of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.

Copies of the statement are available from the NIH Office of Medical Applications of Research, Shannon Bldg., Rm. 216, phone 496-1143, or the NIADDK Office of Health Research Reports, Bldg. 31, Rm. 9A-04, phone 496-3583. ■

# Cancer Institute Launches Public Campaign to Reduce Cancer Deaths

Susan Gerhold

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The National Cancer Institute (NCI) has launched a major campaign to cut cancer deaths in half, by advising Americans to quit smoking and add more high fiber, low fat foods to their diets.

At a press conference held last month at NIH, Health and Human Services Secretary, Margaret M. Heckler, joined Dr. Vincent T. DeVita, Jr., Cancer Institute director, in unveiling a major cancer prevention awareness program.

"Too few Americans realize the simple truth—that cancer is usually caused by the way we live, and its risks can be reduced by the choices we make," Secretary Heckler said.

Research studies show that 80 percent of cancers are linked to life-style and environmental factors. The Secretary stated that the major causes of cancer are the ones that can be controlled. More than 35 percent of cancer deaths are attributable to dietary factors alone and 30 percent are related to smoking.

NCI advises that if Americans quit smoking, at least 75,000 lives could be saved each year, and an additional [illegible],000 lives could be saved through improved diet.

Health and Human Services Secretary, Margaret M. Heckler, faces the press after unveiling a major campaign to fight cancer. With statistics in hand, the Secretary mapped out the strategies planned for the media to notify the general public of preventive measures to curb cancer deaths.

NIH PHOTO 1936

NCI Director Vincent T. DeVita, Jr., MD., answers press questions at the recent conference to unveil a nationwide cancer prevention awareness program.

NIH PHOTO 1937

Based on the most recent scientific information related to cancer cause and prevention, NCI recommends the following:

- Observe workplace safety and health rules, such as using respirators and protective clothing.
- Avoid X-rays unless medically necessary. Discuss the need for them with health providers.
- If you drink alcoholic beverages, do so in moderation—one or two drinks a day.
- Protect skin from over-exposure to sun. Adequate clothing and sunscreens can help reduce the risk of skin cancer.
- For women, take estrogens only as long as necessary.

An NCI national survey showed that 50 percent of those polled failed to identify individual prevention as a way to reduce cancer risk, and 46 percent said they think "there is not much a person can do."

Working through cancer information services at 21 comprehensive cancer centers throughout the country, NCI will distribute pamphlets and messages through a toll-free phone number. This will be followed by a second phase that will aim cancer prevention information at those people most at risk.

"Cancer prevention is our highest goal, but the government cannot do the job alone," said Dr. DeVita. "We need the help of all groups, from neighborhood clubs to major industries, if we are to succeed in reducing cancer deaths." When asked what Americans can do to change their diets, Dr. DeVita suggested replacing fats by eating more whole grain foods, or foods that contain bran or "firm" fruits, such as apples, and vegetables. He also suggested that Americans concentrate on eating lean meats, fish, and poultry as well.

The new prevention booklet can be obtained by calling the toll-free number 1-800-4-CANCER. ■

# Treatment May Not Be Necessary for Women with Hyperprolactinemia

Susan Johnson

"Benign neglect" is the treatment recommended by doctors at NIH for most women with hyperprolactinemia caused by small, nonmalignant tumors of the pituitary gland.

Many physicians recommend surgery for these women, based on the assumption that the tumors will grow over time to a large, potentially troublesome size. A study at NIH, however, has shown that this rarely happens.

Hyperprolactinemia, or an abnormally high level of the hormone prolactin, is often accompanied by menstrual disturbances or the secretion of a milky fluid from the breasts, or both. Some women with hyperprolactinemia stop ovulating and cannot become pregnant.

Prolactin levels normally rise during pregnancy and stay elevated for a few months after delivery. During these periods, the hormone helps prepare the breasts for lactation and initiates milk secretion in breastfeeding mothers. Prolactin levels fluctuate during the day in all adults, rising temporarily in response to stimuli such as sleep, exercise, eating, stress, and coitus. Consistently elevated prolactin levels in nonpregnant women who have not recently had a baby, however, are abnormal.

Hyperprolactinemia can result from the use of certain drugs, including tranquilizers and antihypertensives, or from a number of disorders. The most common cause of non-drug-induced hyperprolactinemia are pituitary tumors that produce prolactin (prolactinomas). Most of these tumors are small, less than 1 cm. in diameter.

It is not known whether small prolactinomas naturally grow to a larger, potentially troublesome size or remain stable. It is known, however, that surgical treatment of hyperprolactinemia is much more successful when the tumor is small. With this in mind, many doctors recommend prompt surgical removal of small prolactinomas, even though they are not causing the patient any serious problems.

A team of NIH scientists supervised by Dr. Lynn Loriaux of the National Institute of Child Health and Human Development (NICHD) did a follow-up study of 25 women with long-standing, untreated hyperprolactinemia. None of the women had taken drugs, other than oral contraceptives, known to increase prolactin levels, and none had medical conditions, other than pituitary tumors, associated with hyperprolactinemia.

When the women were initially evaluated years before, 22 were amenorrheic (had stopped menstruating) and 19 complained of breast secretions. These symptoms predated the follow-up study by an average of 11 years. None of the patients suffered vision defects or other serious complications of large tumors. The average prolactin level among the women was 225 ng/ml, which is six times greater than normal.

From X-rays taken at the initial evaluations, the investigators concluded that 18 of the women had small prolactinomas and seven had large tumors. "We did not surgically confirm the diagnosis of prolactinomas, so we cannot be certain of the true incidence of tumors in our patients," said Dr. Michele Koppelman, NICHD, the coordinator of the research team. She pointed out, however, that the women in the NIH study are representative of the patients with hyperprolactinemia currently being treated with surgery, drugs, or radiation.

None of the women studied had undergone surgery or radiation therapy for their tumors. Five patients had received short courses of bromocriptine, but not for at least 2 months before the follow-up evaluation. Bromocriptine is a drug that lowers prolactin levels, restores fertility, and often shrinks the tumor. These effects last, however, only as long as the drug is administered.

By the time of their follow-up evaluation, seven of the 22 amenorrheic women had started menstruating again, and breast secretions had stopped in six of the 19 women with this problem. Two women had developed breast secretions since their initial evaluation. Nine of the women studied had become pregnant a total of 13 times. Five of the pregnancies were induced by bromocriptine or other drugs, and eight conceived without medical help.

Prolactin levels had dropped in most of the women with small tumors. They went up in only four women, three of whom had large tumors. The average prolactin level for the group had dropped from 225 ng/ml to 155 ng/ml.

X-rays were performed on all of the women at their follow-up evaluations, and were compared to those taken years before. Based on these X-rays, the researchers concluded that tumor size was unchanged in 22 of the women, had decreased in two, and had increased slightly over a 9-year period in one woman.

A newer, more sensitive technique for detecting prolactinomas, the CAT scan, was performed on 23 of the women at their follow-up evaluations. These scans confirmed the X-ray findings.

The physicians concluded from their study that hyperprolactinemia has a benign course in most women with small prolactinomas. Large tumors did not develop in any of the women evaluated, even with the stimulus of pregnancy. Prolactin levels fell in almost all of the women, and symptoms improved in many.

Based on their findings, Dr. Koppelman and her colleagues recommend close monitoring rather than surgical or drug treatment of women with hyperprolactinemia. "Tumor-directed therapy should be reserved for patients with tumor growth or neurological complications of the tumor," said Dr. Koppelman. "We see no reason to subject women to even long-term drug therapy when there is no evidence of tumor progression and the patient has minimal symptoms."

Dr. Koppelman and her colleagues Drs. Loriaux and Kenneth Rieth of NICH and Drs. Myles Jaffe and Rafael Caruso of the National Eye Institute, reported their findings in the January, 1984 issue of the *Annals of Internal Medicine.* ■

# Efficacy of Routine Ultrasound Screening in Pregnancy Unproven, NIH Panel Finds

tricia Blessing

Ultrasound imaging in pregnancy should be limited to situations in which there is an accepted medical reason for the procedure, concluded a panel of experts meeting recently at NIH. The panel said it could not endorse routine ultrasound screening of pregnant women, because there is not enough evidence that routine screening benefits either the mother or the fetus.

Ultrasound imaging uses high-frequency sound waves to produce an image of the fetus and its surroundings on a screen. Doctors use the procedure to evaluate fetal growth and activity, to detect multiple pregnancies and physical abnormalities, to determine fetal age, and for many other purposes. The use of ultrasound in obstetric practice has grown rapidly in the United States. The procedure is now available in nearly all hospitals, and many obstetricians have ulstrasound equipment in their offices.

Concerns about the safety and efficacy of the procedure prompted NIH and the Food and Drug Administration to sponsor a conference, held Feb. 6–8, to assess the use of ultrasound during pregnancy. For almost a year before the conference, a panel headed by Dr. Fredric Frigoletto of the Brigham and Women's Hospital in Boston reviewed the scientific literature and research related to the use of ultrasound during pregnancy.

The panel concluded that ultrasound evaluation can improve the outcome of high-risk or complicated pregnancies. It listed more than two dozen situations in which the procedure can be beneficial. For example, it can be used to identify the cause of vaginal bleeding during pregnancy, or to evaluate fetal growth in pregnancies complicated by diabetes, hypertension, or other disorders.

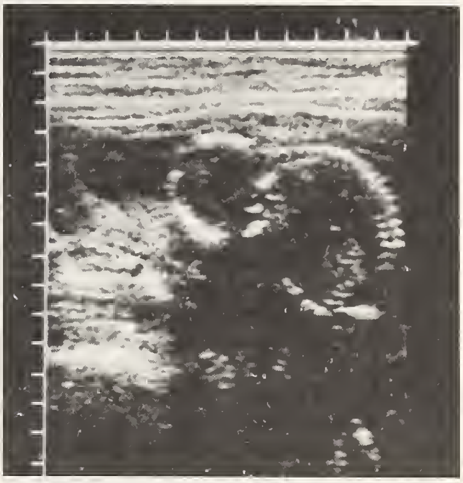
The efficacy of routine ultrasound screening in pregnancy, however, has not been proven, said the panel. It recommended that a randomized clinical study be conducted to determine whether screening improves pregnancy outcome.

The panel also concluded that there is not sufficient information available to reliably assess the risks of ultrasound. While it is encouraging that no harmful effects to either mother or fetus have been reported in more than 20 years of use, it is likely that any ill effects would be subtle and delayed in expression.

Many of the studies reported to date on the safety of ultrasound in humans have been "inadequate," said the panel members. They noted, however, that several studies have shown there is no association between ultrasound exposure and low birth weight or hearing loss.

Animal and cell culture studies have suggested that ultrasound exposure can retard fetal growth, impair the immune response, and produce cell damage and chromosomal changes. Most of these studies involved higher levels of ultrasound energy than are used in diagnostic evaluations, and some of the findings could not be reproduced by other investigators, said the panel. Nevertheless, the reported effects cannot be ignored.

To help answer questions about the safety of ultrasound in pregnancy, the panel recommended that animal studies designed to detect the long-term effects of *in utero* ultrasound exposure be conducted. From these studies, scientists could develop reasonable estimates of the risk from diagnostic ultrasound. ■



Ultrasonogram of 18-week old fetus shows outline of head at left with spinal column curving downward to the right. (Legs are in tight fetal position and therefore are not outlined.)
NIH PHOTO 1938

Dr. Steven Warsof performs an ultrasound examination on a pregnant woman at Georgetown University Hospital in Washington, D.C.
NIH PHOTO 1939

# NIH Panel Recommends Thorough Evaluation Before Treating Insomnia

Marilyn Sargent

Serious insomnia is typically a symptom of some underlying medical or psychiatric problem and signals the need for a complete diagnostic evaluation before treatment is rendered, reported the consensus panel at the National Institute of Mental Health (NIMH)-NIH conference on drugs and insomnia held recently.

When a sleep-promoting medication is indicated, benzodiazepines are the preferred treatment, the panel declared, but such treatment should involve "the smallest effective drug dose for the shortest time necessary."

Moreover, the experts emphasized that a comprehensive treatment plan involves consideration of both psychotherapeutic and behavioral approaches.

The conference sought consensus, based on the latest research, to guide physicians in the day-to-day treatment of insomnia.

After 1½ days of reports on research from 13 scientists and much discussion, the 13-member panel labored through a sleepless night to produce the consensus statement on insomnia. Their efforts were greeted with rousing applause when the statement was read to conference participants by Dr. Daniel Freedman, Director, Division of Adult Psychiatry, and Vice Chairman, Department of Psychiatry, Neuropsychiatric Institute, UCLA, who chaired the meeting.

Participants lauded the panel in particular for defining three broad categories of insomnia—transient, short-term, and long-term. Since the meaning of transient insomnia had been debated throughout the conference, the panel's distinction between transient and short-term insomnia was viewed as especially helpful.

Transient insomnia, concluded the panel, afflicts "normal sleepers who experience acute stress for several days—such as during a brief hospitalization—which causes sleep to be adversely affected." Short-term insomnia, on the other hand, may last up to 3 weeks and is typically related to a stressful situation, such as loss of a loved one, work or family problems, or medical illness.

Long-term insomnia was defined by the researchers as lasting months and years. This category includes people with underlying psychiatric and medical conditions, those who abuse or depend on alcohol or drugs, and those with sleep disorders such as myoclonus (periodic leg movement), 24-hour rhythm disturbances (advanced or delayed sleep phase), or psychophysiological insomnia (no apparent psychiatric or medical syndrome).

Because sleep disorders have many causes, the panel emphasized the need for careful diagnoses involving assessments of sleep habits, daytime sleepiness and functioning, and physical and psychological conditions. In certain cases, referral to a sleep clinic or laboratory tests would prove useful, they said.

In view of the frequent association of psychiatric problems with insomnia, Dr. Anthony Kales, Professor and Chairman, Department of Psychiatry and Director, Sleep Research and Treatment Center, Pennsylvania State University College of Medicine, placed particular importance on the need for psychiatric asessment in cases of chronic insomnia.

For transient and short-term insomnia, the panel recommended that doctors acquaint patients with "good sleep hygiene," such as increased daytime exercise, and reduced use of caffeine, cigarettes, and alcohol. They also suggested relaxation/biofeedback training and other nondrug procedures that can help induce rest.

While they agreed that "sleep-prompting medications may be considered" for transient insomnia, the panel noted differences of opinions among sleep experts about the use of drugs.

For example, Dr. William Dement, Director, Sleep Disorders Center, Stanford University School of Medicine, said that hypnotics (sleep-promoting medications) could be helpful when daily performance suffers from sleep loss caused by jet lag, change in work shift, or short-term stress. Others held that such medications should be reserved for more serious sleep problems.

For long-term insomnia, the panel recommended that nondrug strategies (sleep hygiene and behavioral approaches) be used initially, perhaps with a short trial (less than 1 month) of a hypnotic drug. If patients respond well to the medication, intermittent use (such as one night in three) and gradual discontinuance after 3 or 4 months was suggested.

In those cases when 24-hour circadian rhythm—a cycle of biologic variations—or workshift problems put individuals out of synchronization with the general population, the panel advised chronotherapy, a treatment designed to shift patients' sleep patterns gradually.

When an underlying psychiatric or physical condition is identified, treatment should be targeted to the primary disorder, such as depression, anxiety, or ailments involving circulation, arthritis, metabolism, kidney, or heart. Such treatment often clears up the insomnia, but if sleep problems persist, an adjunct of sleep-promoting medication may be required.

Antidepressants—agents used in treating depression, e.g., monoamine oxidase inhibitors—may provide a useful alternative to benzodiazepines (the parent compound for a number of moo[illegible] altering agents), in some cases of long-term insomnia, according to the consensus report. Dr. Robert Rakel, Professor and Head of the Department of Family Practice, University of Iowa, suggested to the panel that antidepressants, which have less addictive potential than benzodiazepines, may become increasingly useful for aging patients, many of whom experience chronic diseases that prevent sleep.

Benzodiazepines, when used properly, are safe for most people, particularly compared with barbiturates, but there are situations when their use should be avoided. These drugs can prove dangerous for people with sleep apnea, a condition in which the sleeping person actually stops breathing for short periods and then resumes breathing during awakenings that are so brief they may not be remembered. Symptoms of this disorder include daytime drowsiness and heavy snoring. Apnea is most often found in the obese and the elderly; laboratory tests in a sleep clinic are recommended for those suspected of having this problem.

Benzodiazepines should be prescribed for the elderly only with great care, warned Dr. John Rowe, Associate Professor and Director, Division o[illegible] Aging, Harvard Medical School. In his report to the panel, he pointed out that sensitivity to hypnotics tends to increase as the aging process triggers changes in metabolism and renal function and "poorly understood changes in the brain." He particularly warned against prescribing long-acting hypnotics for older patients.

Rowe also cautioned that, while the elderly experience more sleep disturbances than do younger people, practitioners cannot assume that sleep problems are a normal part of aging. Insomnia in the elderly, as in other age groups, often signals a medical or psychiatric problem which must be treated appropriately.

Benzodiazepines also can be dangerous when used with alcohol, particularly if taken shortly after drinking, noted Dr. Edward Sellers, Professor of Pharmacology and Medicine, University of Toronto. "Alcohol seems to prime the liver, and probably the brain, to increase drug interactions and concentrations." In addition to the risk of drug overdose, there is the danger of automobile or industrial accidents because "people do not appreciate the degree of impairment they have when they mix alcohol and drugs," sai[illegible] Sellers.

All participants agreed that benzodiazepines should not be prescribed for patients who are known drug abusers or who tend to become drug-dependent.

According to a 1981 national survey of drug use cited at the conference, some insomnia sufferers who might be helped by medication do not take them. Dr. Glen ellinger, Director, Institute for Research on Social Behavior, Oakland, Calif., reported that 17 percent of those surveyed had been seriously bothered by sleep problems, but only 10 percent of this group had taken a prescribed medication for insomnia during the previous year; 7 percent had tried an over-the-counter compound for sleep (generally considered ineffective for prolonged insomnia).

Dr. Mitchell Balter, NIMH, noted that in a separate survey, physicians in private practice reported that they seldom applied the diagnosis of insomnia. However, when they did diagnose insomnia, 92 percent of patients were prescribed medication.

Dr. Peter Hauri, Director, Dartmouth Sleep Disorder Center, said,"After spending 10 years in research time trying to find an alternative to drug treatment, I have come to the conclusion that serious insomniacs will need a hypnotic at some time to go along with other treatments."

Some people actually are vulnerable to insomnia, he continued. If a stressful period causes them a few sleepless nights, these individuals become so anxious about not sleeping that they cannot relax enough to sleep. To break this cycle, Hauri said, he prescribes hypnotics for a brief period of time and then uses behavioral approaches, such as teaching relaxation techniques. However, if his patients later experience episodic stress and resulting sleeplessness, he recommends that they take a sleeping pill at once before they relearn the bad sleep habits.

After listening to extensive discussion of the pros and cons of long- and short-acting benzodiazepines, the consensus panel highlighted the differences in pharmacological effects of the drugs and recommended that physicians prescribe the drugs on the basis of their specific properties in accordance with a given clinical situation and the patient's needs.

According to the panel, significant risks associated with the use of short-acting benzodiazepines include occasional memory loss the following day, and in cases when the drug is used for prolonged periods, unwanted tolerance and decreased hypnotic effect results. Another problem is the possible return of sleep disturbance when the drugs are discontinued, which might reinforce a patient's belief that the drugs are necessary for satisfactory sleep. The panel agreed that, if benzodiazepines are abused for prolonged periods and abruptly discontinued, withdrawal could be severe.

Long-acting benzodiazepines, said the panel, are more apt to produce unwanted daytime sedation and to accumulate in the body when used chronically. Many patients may experience impaired cognitive or psychomotor skills if they take the drug over a period of weeks. Impaired performance, which often occurs the day after taking a long-acting benzodiazepine, may be potentially hazardous for people in occupations requiring high levels of visual-motor coordination.

Aged patients and people with renal or hepatic dysfunction are more likely to develop cognitive and motor impairments with long-acting benzodiazepines. Ataxia (failure of muscular coordination) and problems with memory and thinking are possible complications.

"Physicians should educate and monitor patients to reduce the risks of dependence, side effects, and possible withdrawal difficulties," the panel concluded. ■

# Antibody Response to Herpes Simplex Virus May Predict Prognosis in Oral Cancer

ody Dove

Evidence has accumulated to suggest a connection between the herpes simplex virus type 1 (HSV-1) and cancer of the mouth.

Previous studies conducted by Dr. Edward J. Shillitoe, formerly of the University of California, San Francisco School of Dentistry, have shown that patients with squamous cell carcinoma of the mouth—a cancer arising from the lining of the mouth—have higher levels of antibody to herpes simplex virus type 1 than do matched controls. Now, in a follow-up study, under a grant from the National Institute of Dental Research, (NIDR), Dr. Shillitoe and colleagues have demonstrated that pre-treatment assessment of the antibody response to HSV-1 is an accurate predictor of survival.

Cancer of the mouth accounts for about four percent of all cancers that occur annually in the United States. Dr. Shillitoe, now at the University of Texas Health Science Center in Houston, stressed that people who get recurrent herpes infections are no more prone to developing oral cancer than people who never had herpes. While cancer of the mouth has been detected in men and women of all ages, it is most frequently found in men after the age of 40. Many studies have shown a significant link between mouth cancer and the use of smoking or chewing tobacco, and snuff, and indicate that the death rate from mouth cancer is about four times higher for cigarette smokers than for nonsmokers. Cancers of the mouth cause about 9,000 deaths annually in this country. However, more than half of all mouth cancer patients are alive five years after treatment, with an improved survival rate when lesions are localized and have not spread.

In Dr. Shillitoe's earlier studies, patients included those with primary herpes simplex virus infection, those with recurrent herpes simplex virus infection, patients with untreated oral cancer, and patients with treated oral cancer. Patients from those studies then entered into a long-term survival study and have now been followed from four to five years. The latest results have been derived from monitoring 70 of these patients who, at the beginning of this study, had untreated squamous cell carcinoma. Levels of IgG, IgA, and IgM antibody to herpes simplex virus type 1 and cytomegalovirus were measured in these patients prior to their receiving treatment.

Dr. Shillitoe found that patients whose pre-treatment level of IgG antibody to HSV-1 was higher than the median had a five-year survival rate of 76 percent. Those whose IgG response fell below the median level had a five-year survival rate of only 44 percent.

The reverse was true for the IgM antibody levels. Patients with IgM antibody levels higher than the median level had a five-year survival rate of 56 percent, while those whose IgM antibody response was lower than the median level had an 81 percent survival rate. Moreover, patients with untreated oral cancer had higher levels of IgM antibody than did either patients with acute or recurrent herpetic infections or age-matched control subjects. Patients who had been treated successfully for oral cancer more than one year earlier did not have higher levels of IgM antibody to herpes simplex virus type 1. These findings are consisent with the hypothesis that cancer of the mouth is associated with expression of HSV-1 antigens that stimulate IgM rather than IgG antibody responses.

No relationship was found between high or low levels of IgA antibody and survival rates.

When survivals were compared to pre-treatment tumor size, patients with the smallest tumors had a survival rate of 75 percent, while those with the largest tumors had a survival rate of 57 percent. Pre-treatment assessment of antibody to herpes simplex virus type 1 therefore distinguished the prognosis of the cancer as accurately as tumor staging (determination of the degree of advancement of a tumor, e.g. whether it is localized or metastatic). ■

# Older Women May Benefit From Estrogen Replacement and Additional Calcium to Prevent Osteoporosis

Barbara Weldon

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"The mainstays of preventing and managing osteoporosis are estrogen and calcium," according to an NIH Consensus Development Panel. During a three-day conference, the panel said that estrogen and calcium deficiencies are the major causes of primary osteoporosis, an age-related disorder characterized by decreased bone mass, which makes the bones more susceptible to fracture.

The conference, sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) and the NIH Office of Medical Applications of Research, was held April 2–4, in Bethesda.

In order to prevent osteoporosis, the 14-member panel recommended estrogen replacement in postmenopausal women; adequate nutrition, including an elemental calcium intake of 1,000 to 1,500 mg a day; and a program of modest weight-bearing exercise such as walking.

Panel Chairman Dr. William E. Peck, Professor of Medicine, Washington University School of Medicine and the Jewish Hospital of St. Louis, said that osteoporosis is a major health problem that affects some 15–20 million Americans, and costs the nation at least $3.8 billion per year.

The panel said that at the present time there are few established laboratory tests for identifying persons at risk for osteoporosis or those with mild disease. Generally, a fracture must occur before a positive diagnosis can be made.

Osteoporosis is a subtle disease, which may appear without warning. A fall, blow, or lifting action that would not strain the average person can easily cause one or more bones to break in a person with severe osteoporosis. Although any of the bones may be affected, fractures of the spine, wrist, and hip are the most common.

It is estimated that about 1.3 million fractures attributable to osteoporosis occur in people 45 years of age or older. Among those who live to be age 90, one-third of women and 17 percent of men will suffer a hip fracture due to osteoporosis. The panel reported that most older patients with hip fractures fail to recover normal activity. Moreover, mortality within one year after fracture occurs in approximately 20 percent of patients.

The risk of osteoporosis is great among postmenopausal Caucasian women. Removal of the ovaries by surgery or damage from irradiation or early natural menopause are strong predictors for the development of the disease. Postmenopausal women are especially vulnerable because changes in the body's hormone levels accelerate loss of bone tissue. Women who are underweight are more likely to develop osteoporosis, and cigarette smoking may also be a risk factor.

The panel suggested that in order to retard or halt the progress of the disease before structural defects occur, the following strategies are warranted:

- Estrogen replacement therapy—low-dose estrogen is a highly effective method for the prevention of osteoporosis in women. Case-controlled studies have shown a substantial reduction in hip and wrist fractures in women whose estrogen replacement began within a few years of menopause. Even when initiated as late as six years after menopause, estrogen prevents further loss of bone mass. However, it does not restore it to premenopausal levels. Estrogen is associated with increased risk of endometrial cancer, an uncommon form of cancer that, fortunately, is easily detected and rarely fatal. However, the panel felt the consequences of osteoporosis are far greater than the risks of endometrial cancer. Most studies do not link estrogen to increased breast cancer risk. Until more data on risks and benefits of estrogen therapy are available, some physicians and patients may prefer to reserve estrogen therapy for women who have undergone premature menopause or have other risk factors.

This X-ray shows a fractured hip due to osteoporosis in a 77-year-old woman. (Photo courtesy William W. Scott, Jr., M.D., Johns Hopkins School of Medicine)

NIH PHOTO 1940

- Increased calcium intake—the usual daily calcium intake in the United States of 450 to 550 mg falls below the National Research Council's recommended dietary allowance of 800 mg. In addition, the osteoporosis panel recommended a daily requirement—above that of the recommended allowance—of 1,000 mg of calcium for premenopausal and estrogen-treated women and 1,500 mg daily for postmenopausal women not on estrogen. Increased calcium intake may also prevent age-related bone loss in men. The major sources of calcium in the U.S. diet are milk and dairy products. For people who are unable to take 1,000 to 1,500 mg of calcium by diet, calcium supplement tablets are recommended. Anyone with a history of kidney stones should take calcium supplements only under the guidance of a physician.
- Normal levels of vitamin D, especially for people who get little sunlight—because vitamin D is dangerous at high doses, one should not take more than 600 to 800 I.U. (twice the recommended daily allowance) without a doctor's recommendation.
- Weight-bearing exercise—some recent studies suggest that weight-bearing exercise, such as walking, may reduce bone loss.

(Photo courtesy of the National Institute on Aging) NIH PHOTO 1941

The panel said that prevention of fractures is the primary goal in the approach to osteoporosis. "There is great need for additional research on understanding the biology of human bone, defining individuals at special risks, and developing safe, effective, low-cost strategies for fracture prevention," they said.

The panel members included representatives of orthopedics, endocrinology, gynecology, rheumatology, epidemiology, nutrition, biochemistry, family medicine, and the general public.

Copies of the consensus statement are available from the NIH Office of Medical Applications of Research, Shannon Building, Room 216, phone 496-1143, or the NIADDK Office of Health Research Reports, Bldg. 31, Room 9A04, phone 496-3583. ■

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# Dental Sealants Found Effective in Protecting Against Tooth Decay

Jody Dove

Citing unequivocal evidence as to their effectiveness and safety, an NIH Consensus Development Panel has recommended widespread use of tooth sealants in millions of children to offer increased protection against tooth decay (dental caries). Sealants are currently underused in private and public dental health care delivery systems. The panel urged that "intensive efforts be undertaken" to increase their use.

The conference, "Dental Sealants in the Prevention of Tooth Decay," was jointly sponsored by the National Institute of Dental Research (NIDR) and the NIH Office of Medical Applications of Research. The Consensus Development Panel consisted of biomedical investigators, dentists in private practice and in public health programs, academicians, a dental hygienist, and representatives from public interest groups.

Before making their recommendations, the panel heard a day and a half of scientific presentations from experts who addressed these key questions:

With the current widespread use of fluorides and the generalized decrease in caries experience among children, is there a need for sealants?

How effective are sealants?

Are there risks associated with the use of sealants?

What are the indications for using sealants in individual and community-based caries preventive programs?

What are the clinical procedures involved in successful sealant application, and what training and education are required?

What factors have influenced and should influence the adoption and utilization of sealants for caries prevention?

What is the current status of sealant research and what should be the research priorities for sealants and their implementation?

The panel stated that the use of sealants in addition to fluorides would substantially reduce the occurrence of dental caries in the U.S. population. Results published from the 1979–80 National Dental Caries Prevalence Survey (coordinated by NIDR) indicate that tooth decay among school children has decreased markedly during the past decade largely because of access to fluorides through community water fluoridation, school-based fluoride mouthrinse and tablet programs, and fluoride toothpaste. Fluorides are mainly effective on the smooth surfaces of teeth, but most cavities occur on the chewing surfaces that have pits and fissures where food and bacteria become trapped.

Applying sealants—clear plastic films—to the chewing surfaces of teeth effectively guards against decay. Research findings over the past 15 years have consistently demonstrated that sealants provide 100 percent protection when retained on the tooth. The application of sealants is a painless procedure, involving no loss of tooth structure.

The panel strongly urged that all patients and parents be made aware of the availability of sealants, and that appropriate use be encouraged. Those individuals who can benefit most from the treatment are children with newly erupted molar teeth.

Dentists, dental hygienists, and dental assistants trained in the procedure can apply sealants. The plastic films may be placed on both primary (baby) molars and on permanent molars. Currently, there are three types of sealants, named according to the method by which they are cured (hardened)—chemical or self-cured, ultraviolet light-cured, and visible light-cured.

The application of sealants is a simple procedure. First, the chewing surfaces of molars are cleaned and dried. Next, the surfaces are etched with a mild phosphoric acid solution to improve adhesion. The teeth are washed and thoroughly dried, with care taken to avoid contamination by saliva. The sealant is then placed on the prepared surfaces and cured to hardness.

With the research findings overwhelmingly pointing to the benefits of sealants, the panel now urges practitioners, dental health agency directors, and dental health educators to incorporate the use of sealants into their practices and programs. ■

# Biochemical Markers Useful in Preventing Cancer and Cardiovascular Disease Developed at the Clinical Center

Sheila Munson

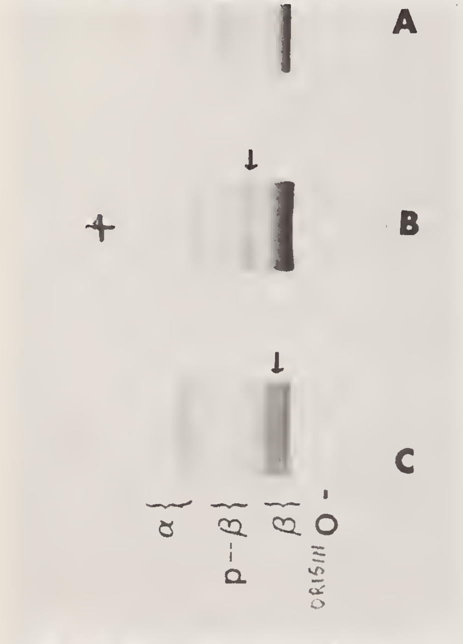
Cancer and cardiovascular diseases—including heart attacks and strokes—are the major causes of death and disability today. In both types of disorders, researchers note that biochemical abnormalities exist long before the onset of symptoms of the disease.

Dr. Nicholas Papadopoulos of the Clinical Pathology Department, Clinical Center (CC), has developed two tests that aid in the diagnosis of cardiovascular disease and cancer.

The test for cardiovascular disease involves determining lipoproteins (complex molecules that transport fat in the blood) by high-resolution electrophoresis. The test for cancer involves separating serum proteins by the same high-resolution electrophoresis, and identifying them by another variation of electrophoresis, called immunofixation.

Some circulating lipoproteins have been associated with the development of cardiovascular disease. Dr. Papadopoulos' test demonstrates the presence of all lipoproteins as they circulate in a normal state in the blood.

In addition, this test detects two beta lipoproteins that identify patients with type-3 hyperlipoproteinemia as compared to the single beta lipoprotein band found in normal persons. Patients with this condition develop angina and heart attacks early in life. With this test, physicians can begin treatment early. As a result, the levels of lipids will return to normal and the symptoms will be relieved or disappear.



The four lipoprotein electrophoretic patterns show a normolipidemic individual (A), a patient with an extra, slow pre-beta band (B), and a patient with type-3 hyperlipidemia with a beta doublet (C). Arrows indicate lipoprotein bands. NIH PHOTO 1942

Along with screening potential heart attack victims, this laboratory test also demonstrates an extra (pre-beta) lipoprotein fraction found in the serum of a majority of patients with cardiovascular disease and only in a small number of normal individuals.

The extra pre-beta band found in the normal individuals may be an early predictive risk factor for later development of cardiovascular disease. With this information, a physician can observe more closely the potential coronary heart disease patient and prescribe appropriate therapeutic measures to reduce the risk of atherosclerosis which leads to heart attacks and strokes.

Dr. Papadoupolos has also developed a high-resolution agarose gel electrophoresis test for detecting abnormalities of serum proteins which can be used as biochemical markers for cancer.

The standard test used in the laboratory is called zone electrophoresis, a procedure that separates serum proteins into distinct fractions called albumin and alpha, beta, and gamma globulins.

The gamma globulin fraction contains antibodies called immunoglobulins that defend and protect the body from disease.

Different types and changes of immunoglobulins have been associated with a variety of immunologic abnormalities, such as rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and malignant tumors.

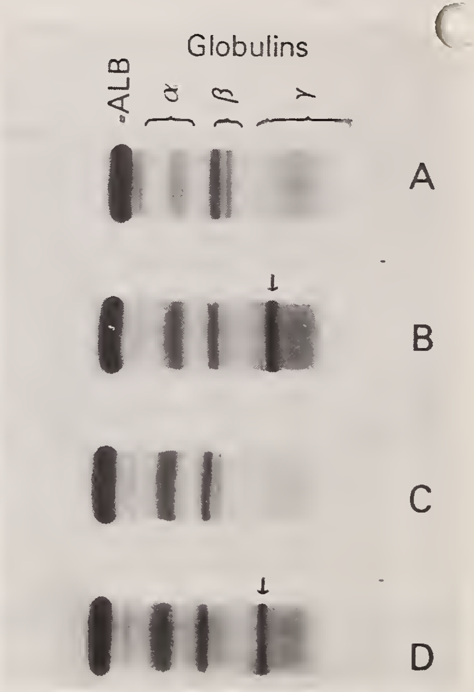
Malignant cells constantly release unique proteins in the circulation, and the concentration of these proteins rises with the progress of the malignant process.

These proteins appear as homogeneous, distinct bands in diffuse gamma globulin zones. The presence of a single prominent band in the normally diffuse gamma globulin zone is often due to conditions called "monoclonal gammopathies" or to malignant transformations of blood cells and tissues.

Dr. Papadopoulos' test is more sensitive than the standard zone electrophoresis method because it can detect strong as well as weak bands (even mini bands) in the gamma globulin region.

Dr. Papadoupolos found that serum protein electrophoretic patterns from patients with lymphoma demonstrated monoclonal bands in the gamma globulin zone as compared to a normal pattern with a diffuse gamma globulin zone.

After surgery, chemotherapy, or radiation, the protein concentration decreases, the band disappears and the diffuse pattern reappears in the gamma globulin region.



Protein electrophoretic patterns are displayed in four series. The first series; A, demonstrates normal serum. B identifies the protein band in a lymphoma patient before chemotherapy and C is after therapy. D shows the protein band upon recurrence of the disease.
NIH PHOTO 1943

The single band may reappear, however, often long before the disease returns clinically. Therefore, the detection and monitoring of the band by standard zone electrophoresis serves as a biochemical marker for the detection and prediction of an abnormal or malignant process.

These inexpensive and non-invasive laboratory tests are significant because they will enable the physician to diagnose a disorder early and prescribe appropriate therapy to minimize or eliminate the threat of disease.

Dr. Papadopoulos also found that these sensitive tests can be used in patients with multiple sclerosis, AIDS, and autoimmune diseases such as lupus, myasthenia gravis and vasculitis. He also hopes that this laboratory procedure can be used more fully to screen high risk individuals who are currently asymptomatic, and in clinical trials, Health Maintenance Organizations (HMO's), and Lipid Clinics throughout the country.

For further information, contact Dr. Papadopoulos, Building 10, Room 2C433, NIH, Bethesda, Maryland 20205 or call (301) 496-1924. ■

# Researchers Relate Liver Failure to Brain Dysfunction

Linda Stalvey

Clinicians over the last several decades, and perhaps as long as the past one hundred years, have been immensely interested in an apparent link between liver and brain function. When diseases of the liver cause liver failure, distinct neurologic symptoms occur ranging from disturbances in sleep patterns and personality changes to coma.

Several theories have been proposed to explain the link in liver/brain function. Three of these theories have received much attention.

When the liver shuts down or its function is impaired, several substances that can affect the function of the brain, which are normally cleared by the liver, acumulate in the blood and may eventually cross the blood-brain barrier into the brain. One hypothesis suggests that accumulation of ammonia (a normal waste product that typically is disposed of easily) may be the cause of neurologic problems associated with liver disease.

Another suggests that the additive effects of ammonia, mercaptans, and fatty acids affect the functioning of the brain. The third hypothesis, termed the false neurotransmitter hypothesis, suggests that the substances that normally conduct nerve transmission in the brain (neurotransmitters) are reduced, while "false" neurotransmitters increase. The overall effect of this upset balance is thought to lead to the neurologic problems evidenced in liver disease/failure.

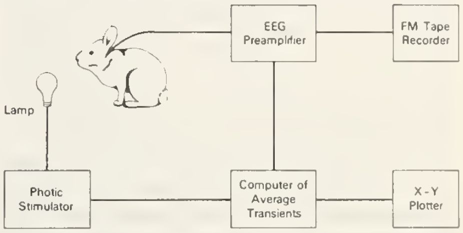
Now researchers in the Liver Unit at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), Drs. E. Anthony Jones, S. Chris Pappas, and Peter Ferenci, propose a different hypothesis, with supporting data to explain the functional relationship between the liver and the brain.

This hypothesis has been termed the true neurotransmitter, or GABA, hypothesis. GABA, gamma-aminobutyric acid, is the principal substance that causes inhibition of neural function in the mammalian brain. This hypothesis suggests that increased levels of GABA in the blood, together with an increased sensitivity of the brain to GABA, eventually leads to neurologic dysfunction.

Using a rabbit model of liver failure, the investigators examined visual evoked potentials (VEPs). VEPs are the averaged recorded brain responses to multiple light pulses by an animal undergoing certain treatments. The investigators found that the VEPs in liver coma were very similar to those caused by stimulation of the GABA neurotransmitter system, whereas responses to ammonia and ammonia with other toxic substances were different.

Other data indicate that GABA in the bloodstream can cross into the brain during liver failure, while under normal circumstances it does not; that it is produced by bacteria in the gut; and that brain receptors for GABA increase in the case of liver failure-induced coma.

These results are exciting and research continues to strengthen the hypothesis. With the eventual development of new drugs, it may be possible to counteract the inhibitory brain effects of GABA in coma due to liver failure. ■



**Using a rabbit model, the researchers can examine recorded brain responses to light pulses from a lamp. They found that visual evoked potentials (VEP's) in liver coma were similar to those caused by the stimulation of the GABA neurotransmitter.**

NIH PHOTO 1944

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# Diet Can Affect Sleep Stages in Newborns

Susan Johnson

The composition of a newborn's diet can influence the amount of time it takes the infant to fall asleep after a feeding, according to a recent study supported in part by the National Institute of Child Health and Human Development (NICHD). The study was designed to investigate whether dietary components can affect sleep behavior in newborns.

Researchers at Harvard Medical School and Boston University School of Medicine have found that the stages in a newborn's sleep pattern can be affected by two amino acids—trytophan and valine. Twenty healthy, bottle-fed newborns (2–3 days of age) were involved in the study. The babies were divided into two groups. In one group, for their evening feeding, the infants were given regular commercial formula alternating with trytophan solution; in the other group, the evening feedings consisted of commercial formula alternating with a solution containing valine. Thus, the effects on sleep patterns of tryptophan and valine, respectively, could be compared with the effects of regular formula.

According to the study, when fed the tryptophan solution the babies entered the active sleep stage an average of 14 minutes earlier, and the quiet sleep stage 20 minutes earlier, than after a feeding of regular infant formula. The onset of active and quite sleep stages in the newborns fed the valine solution, took an average of 16 and 39 minutes longer, respectively, in comparison to the onset of these stages after a commercial formula feeding. In other words, the infants fell asleep faster after a feeding of tryptophan solution than they did following a feeding of regular formula; but, regular formula was more effective in producing earlier sleep than was valine solution.

Newborns go through several sleep stages that can be measured by their behavior. Typically, a newborn enters sleep through active sleep—a period of rapid eye movement, frequent body movement and irregular respiration. This stage is followed by quiet sleep where the infant's eye movements are no longer visible, respiration is regular and body movements are minimal. The third stage is a combination of quiet and active sleep. The other stages include drowsiness, wakefulness and fretting, or crying.

Trytophan is essential for the synthesis and release of serotonin, a neurotransmitter in the brain which is believed to be partially responsible for regulating sleep behavior in humans. Trytophan is found in breast milk and infant formulas, as well as in high protein foods like milk, poultry, and eggs.

The amount of tryptophan and valine delivered to the brain is affected by the concentration of these amino acids in the blood. Valine and tryptophan compete for the same carrier mechanism that allows their entry into the brain. Therefore, if there is more valine at the site than tryptophan, the valine will monopolize the carrier and decrease the amount of tryptophan transported into the brain.

The researchers, Drs. Michael Yogman and Steven Zeisel, say this study demonstrates that the onset of newborn sleep stages can be influenced by diet without disrupting the normal pattern of falling asleep. Although adults and newborns have different sleep pattern organizations (adults enter sleep through the quiet stage), similar effects on the onset of sleep have been produced in adults by modifying dietary components, according to the researchers.

They said past research on nutrition and infant behavior has focused on long-term effects. This study, which was reported recently in *The New England Journal of Medicine,* examined the short-term effects of modifying only a single component of the diet on newborn sleep behavior. ■

# New Monitor Allows Evaluation of Hyperactive Children

Judy Folkenberg

A unique activity monitor is helping National Institute of Mental Health (NIMH) scientists verify that hyperactive children are more active than normal children—even during sleep.

Weighing only 2½ ounces, the monitor uses a pair of computer memory chips to record hourly activity levels for up to 240 hours. Worn either in a pouch suspended from a belt or like a wrist watch, the monitor was developed by two NIMH engineers, Drs. Theodore Colburn and Bruce Smith, and two NIMH electronics technicians, Jerry Guarini and Norwood Simmons. It provides a continuous and objective method for measuring the body's activity levels.

In a study conducted by Drs. Linda Porrino and Judith Rapoport and their colleagues in the Intramural Research Program, 24 boys—12 normal and 12 hyperactive—aged 6 to 12 were monitored around the clock for one week. With the aid of their parents, they also kept daily diaries of all their activities, including eating, sleeping, engaging in sports, indoor and outdoor playing, and watching television.

When they analyzed data from the monitors, the researchers found that the hyperactive boys had higher activity levels than normal boys during all activities—from school and playtime to meals and sleep.

Dr. Linda Porrino holds disc containing data obtained by the hyperactivity monitor.

NIH PHOTO 1945

The hyperactivity monitor, which can be worn on the wrist, provides investigators with an objective evaluation of activity levels.

NIH PHOTO 1946

"One of the more surprising and impressive findings of this study was the higher levels of movement of hyperactives during sleep," says Porrino. "Because activity was measured in the home environment, there were no constraints on sleep time and no interference from artificial settings or recording equipment. These findings reflect true differences in activity while asleep rather than differences in actual time asleep."

The study also contradicts the prevailing view that hyperactive children only seem more active than other children.

Commenting on this, Porrino says, "It has been suggested that hyperactives are considered more active than normal children just because their movements are inappropriate (such as constantly jumping out of one's chair in the classroom) and lack distinct direction, which makes their activity seem more salient. The present study seems to refute this. We have demonstrated increasing levels of motor activity of hyperactive boys when compared with control children. While hyperactives may also exhibit qualitative differences in behavior (an issue not addressed in this study), a substantial increase in simple motor behavior is a clear characteristic of this group."

These findings are especially significant because the study had three important advantages over previous studies on hyperactivity, says Porrino. First, children were measured and monitored in the "real world" rather than asked to engage in specific tasks in a laboratory setting. Secondly, their behavior was recorded over a relatively long period of time—longer than previous studies. And lastly, the measurement was objective, with no reliance on the perceptions of outside observers and no interpretive biases. She notes that "motor behavior should be included as an important criterion in the diagnosis of hyperactivity."

In yet another clinical application of the monitor, NIMH's Dr. Thomas Wehr and his associates have monitored and obtained objective measurements of the activity of manic-depressive patients. Differences of up to 500 percent in the levels of motor activity and sleep in manic versus depressive states have been recorded.

"We saw a particular pattern of sleep changes associated with the manic-depressives when they switched from the depressive cycle to the manic or hypomanic cycle," says Wehr. "Individuals who remain awake all night every other night, for one or a series of alternate nights. This precise pattern had not been described previously until the activity monitor detected it."

Not only can the device aid in investigations of disturbances in circadian rhythm (a cycle of biologic variations), but in the diagnosis and evaluation of manic-depressive illness, insomnia, endocrinologic and/or neurologic disorders, and, perhaps most importantly, i observation of normal development and behavior. ■

The monitor can be worn on a belt around the waist.

NIH PHOTO 1947

# MEDICAL CAPSULES

Sandra D. Levine

- Researchers at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) have been conducting studies of multiple sclerosis (MS) in twins to identify the relative influence of genetic and environmental factors in the etiology of this disease.

The cause of MS is believed to be multifactorial, and comparison of identical and fraternal pairs of twins in which at least one twin has MS provides a unique opportunity for analysis of the interplay between genetic and environmental influences.

One recent study, part of ongoing studies of MS in twins, was designed to investigate the cellular immune response to measles virus, long considered a possible cause of the disease.

The study of 28 sets of twins both concordant and discordant for MS, revealed that seven of the 34 affected twins manifested abnormal, elevated responses to the measles virus. The unaffected twins had normal responses.

This finding may be helpful in understanding the immune mechanisms involved in MS.

- Researchers at Rockefeller University in New York have found that women with systemic lupus erythematosus (SLE) have an abnormality in the way their bodies use testosterone, a male hormone that occurs in small amounts in women.

According to the scientists, who are working under a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), women with SLE rapidly convert much of their testosterone into substances that in turn can be converted to estrogen. In this way, testosterone levels are lowered and levels of estrogen are raised.

Because scientists theorize that testosterone may have a stabilizing effect on the immune system, lack of a certain level of testosterone may make some women more likely to develop immune system disorders such as SLE. The researchers had already ascertained that both men and women with SLE demonstrate an abnormal metabolism of the female hormone estrogen.

SLE affects 500 thousand people in the U.S., mostly women of childbearing age.

- The National Institute of General Medical Sciences (NIGMS) is funding research into the role of metals in electron transfer—mechanisms that have broad implications for health, because metals and electron transfer are essential to cellular function.

A major investigator in this area is Dr. Henry Taube of Stanford University, who won the 1983 Nobel Prize in Chemistry for his work.

Electron transfer is involved in many chemical reactions, principally the release of energy for use by the cells of living organisms. Taube is investigating the basic chemistry of how the transfer of electrons occurs in compounds containing metals, such as copper and manganese, and in organic molecules by observing the effect of varying either the metal or the organic material.

This research relates to a wide range of basic processes from the conversion of sunlight to chemical energy during photosynthesis to the chemical reactions in batteries that produce electric current—and even more importantly to an understanding of the function of living cells.

- A treatment that may improve calcium balance and reduce the number of bone fractures caused by osteoporosis has been developed by NIH-supported scientists.

Clinical trials funded by NIADDK have shown that, taken daily, a metabolite of vitamin D called 1, 25-dihydroxyvitamin D improves calcium retention in bone, increases bone volume and reduces bone fractures by 50 to 75 percent.

Osteoporosis affects mainly post-menopausal women and is responsible for major bone fractures in approximately one-third of the population over the age of 70.

- A reduction is smoking during pregnancy improves the birth weight of the baby, according to a recent study.

Results of a randomized clinical trial, supported in part by a grant from the National Institute of Child Health and Human Development (NICHD), were reported in the February 17 issue of the *Journal of the American Medical Association.*

Over a 2½-year period, 935 smokers in approximately their 15th week of pregnancy were randomly assigned to a treatment group or to a control group. Those in the treatment group received assistance to stop smoking through various intervention strategies.

Questionnaires and saliva samples obtained at the time of randomization were compared with those taken during the eighth month of pregnancy. The saliva samples were tested for the level of thiocyanate, which is known to be correlated with the number of cigarettes smoked and provides an objective biochemical marker of smoking. The difference between the two groups in thiocyanate level and reported amount of smoking was statistically significant. This indicates the effectiveness of the anti-smoking intervention provided to the treatment group.

The infants born to mothers in the treatment group (429 single live births) had an average birth weight that was 92 g (about 3.2 oz) heavier than those in the control group (438 single live births). The babies in the treatment group were also significantly greater in length.

The findings from this study, therefore, demonstrate that a reduction in smoking even *during* pregnancy has a favorable effect on fetal growth.

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May–June 1984

Today, more than one million individuals, 65 years and older, require long-term care, frequently provided by nursing homes. Many factors, such as an increasing number of elderly people, have converged to render old patterns of care in these institutions unresponsive to current needs.

At a recent conference experts discussed the innovative concept of the "teaching nursing home". At these facilities, researchers will conduct studies on patient management and chronic diseases. It is hoped that research and teaching will save more lives and cut costs. See page 10.

Congenital rubella, or German measles, normally a mild disease, can have a devastating impact on the fetus, causing birth defects such as cataracts, mental retardation and hearing impairments.

At an international conference scientists discussed the effectiveness of the vaccine and raised several important questions. For instance, little is known about the rubella antibody and the level of antibody protection required for immunity. See page 8.

A recent symposium sponsored by the NIH on the use of animals in research brought together a variety of experts to discuss the ethical, scientific and institutional concerns relating to this issue.

The Public Health Service has recently proposed changes in its policy to ensure that animals used in research are adequately protected. Since almost half of NIH research projects involve the use of animals, the proposed changes could have a broad impact on the biomedical research community. See page 6.

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The editorial staff wishes to correct an error in the April issue of *News and Features*. "Efficacy of Routine Ultrasound Screening in Pregnancy Unproven, NIH Panel Finds" which appeared on page 5, was written by Susan Johnson. "Diet Can Affect Sleep Stages in Newborns" which appeared on page 11, was written by Patricia Blessing.

We apologize for the error.

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# Looking at How We Age: The Baltimore Longitudinal Study of Aging

Esther Solomon

Although 71-year-old Jane Coffin is very healthy, she travels to Baltimore from her home in Scientists Cliffs, Maryland once every 2 years and spends 2½ days taking extensive and demanding medical and psychological tests. They include blood and urine studies, electrocardiogram and chest X-ray, immune function tests, skin cell cultures, vision and hearing screenings, and evaluations of kidney, lung, nervous system and other functions. Her body composition is measured to determine the amount of fat as well as the density and calcium content of bone. She takes psychological, memory, learning and reasoning ability tests, gives a detailed sexual and social history and reports her dietary habits.

Ms. Coffin is one of 1000 healthy volunteers between the ages of 20 and 96 years in the Baltimore Longitudinal Study of Aging (BLSA). Scientists are studying their physiological and behavioral changes over the adult life span to distinguish the changes that occur with normal aging from those associated with disease. When Ms. Coffin's father, Dr. W. W. Peter, became the first BLSA volunteer in 1958, most research on aging had been done on sick, institutionalized elderly. Dr. Peter, a retired Public Health Service scientist, persuaded many of his colleagues and friends to volunteer for the study that is now a resource of the National Institute on Aging's (NIA) Gerontology Research Center (GRC).

Learning about physiological and psychological measurements that are normal for specific ages can have far-reaching results. Until recently, for example, up to 50 percent of people aged 60 and older could have been diagnosed as having diabetes mellitus, largely because their blood sugar levels on glucose tolerance testing were higher than those of normal younger adults. However, there were no known adverse effects of these higher blood sugar levels in most of these older people. When BLSA scientists evaluated test results by age, they found that older volunteers normally have somewhat higher blood sugar levels. This is apparently because with aging the body's cells have a decreased sensitivity to insulin and the sugar is therefore removed from the blood at a slower rate.

Based on these and other studies, the NIH National Diabetes Data Group established higher standards for normal blood sugar levels thus reducing the number of falsely positive diagnoses for diabetes.

Ideal adult body weight also seems to depend on age. There is a range of body weights that seems to be associated with longer life but what is too little or too much depends partly on age. BLSA and other studies show that the best weight for younger adults, for instance, is lower than the best weight for older adults. In the latter half of life, there is a survival advantage to weighing somewhat more than the usual tables indicate.

By studying healthy people for many years, scientists can find out how events or conditions occurring earlier in life may relate to changes in intellectual or physiological functions in old age, or to some diseases. Cigarette smoking, for instance, can lead to a seriously shortened life or a symptom-plagued later life. Smoking is associated with lung impairment, cancer, heart disease and other very serious problems. Heavy smokers in the BLSA have lung function capabilities of non-smokers who are about 10 years older. However, within 18 to 24 months after stopping smoking, lung function returns to near normal for the subject's age.

Charting changes with aging in individuals over long periods helps scientists eliminate some of the errors that might occur when comparing older with younger persons. For example, cholesterol levels are higher in middle-aged men and women than in the elderly. It was not known whether this was because those middle-aged people with the highest levels were more likely to die before they reached old age or if there was something about aging that led to an actual decline in cholesterol. Since older volunteers were raised in earlier times, ate different foods and were exposed to different environmental factors, it was possible that those with low cholesterol levels never had higher levels.

Repeated studies of BLSA individuals in the 1960s showed that cholesterol levels rose as young adults moved into old age. However, an important additional change occurred in the 1970s, when subjects of all ages had a significant decline in their cholesterol values—an effect clearly due to environmental influences which overrode the effects of biologic aging processes. Investigators are still

Technician Ed Billips administers a lung function test to BLSA volunteer Jane Coffin. Mrs. Coffin, 71 years old, travels to Baltimore once every two years from her home in Scientists Cliffs, Maryland, a small Chesapeake Bay town on the Western shore. Her father, Dr. W.W. Peter, was the first BLSA volunteer in 1958 and Mrs. Coffin has at least 14 other relatives participating in the study.

NIH PHOTO 1949

Another BLSA volunteer squeezes the hand dynamometer, which measures static hand strength. Many older individuals do well on this test until they reach the age of 65. Investigators note that strength does not decline until after that age.

NIH PHOTO 1950

looking at what environmental factors might account for these changes.

There were also dietary changes over the years in these volunteers. BLSA men and American men in general are eating less saturated fat, more unsaturated fat, and less cholesterol, a more prudent American diet thought to be beneficial in preventing heart attacks.

Many, but by no means all body functions very gradually decline from 30 to 90 years of age. There were wide individual differences in aging, with many older persons performing as well as younger persons on some tests. Sometimes performance improved over time with lifestyle changes—such as adding daily exercise.

Different body systems also vary greatly in rates of change. In general, more complex functions decline more rapidly with age than simple functions. In the musculoskeletal system, for example, there is an earlier and greater decrease in performance when tasks require the coordinated responses of several muscle groups. Strength (isometric) of arm and back muscles declines very slightly until after age 65 in most healthy people, whereas maximum work rate (the ability to stay with an activity over a period of time) begins to fall as early as ages 25 through 30.

Even though regular physical exercise has many benefits, physically active volunteers over age 30 had no greater muscle mass than their peers who did not exercise. When they achieve a leaner appearance from exercise, it is apparently due to fat loss. Some evidence suggests that an overall loss of muscle mass with aging may result from a decreased production of growth hormone, a potent factor in building muscle in youth.

As we age there is a decrease in the bulk of cells in many body tissues and cells grown in laboratory cultures reproduce fewer times before they lose their ability to divide. The loss of cellular mass results in a lower water content in the body. This means that identical doses of some drugs taken by a young and an old person result in a higher concentration in the older person. This is one reason elderly persons require lower doses of many drugs.

Although the aged can metabolize alcohol and some other drugs as efficiently as young adults, older men showed more impairments in reaction time and intellectual functions, such as memory and decision-making abilities, than did younger men with the same blood levels of alcohol.

Nutritional diaries kept by 180 BLSA men showed that they tended to eat less as they grew older. This may be due in part to gradual loss of muscle and other tissue and to the gradual reduction in physical activity with advancing age. There was also a tendency to substitute carbohydrate calories for fat calories in older individuals. This study also showed change from saturated to polyunsaturated fatty acids from the 1960s to the 1970s.

While older people sometimes complain of decrease in the ability to taste, taste sensitivity and saliva flow did not change dramatically with age in healthy, nonmedicated BLSA women and men. The taste decrements which did occur usually were specific to certain taste qualities, such as sensitivity to salt.

Beginning at about age 35, there is a gradual loss of bone mineral which accelerates at about age 50 in both sexes, but much more so in women. BLSA scientists are studying how nutrition, drugs, exercise, hormone changes at menopause and other factors might affect the strength and density of bones. They are especially concerned about osteoporosis and osteoarthritis in women. These diseases can be painful and crippling in their later stages and are significant causes of disability.

Although there are some age-related changes in the heart, BLSA studies using a sophisticated but non-invasive new technique called stress/thallium testing show that when it is healthy, the heart of an older person pumps about as well as that of a younger adult. The size of the

BLSA volunteer Linda Sundergill, receives instructions from technician Constance Strickland (right), about the use of the 24-hour electrocardiography monitor which she is wearing. It measures the electrical currents in the heart muscle just before each heart beat.

NIH PHOTO 1951

BLSA volunteer Ann W. Tuttle applies pressure in a hand grip strength test to measure muscle changes over a period of years.

NIH PHOTO 1952

heart cavity and the strength and speed of the contractions show little change with age. From ages 30 to 80, however, the wall of the left ventricle of the heart grows 25 percent thicker and systolic blood pressure increases about 15 percent. The valve which controls blood flow in and out of the heart opens and closes a little more slowly.

Stress/thallium testing also showed that coronary artery disease (CAD) appears to be more prevalent than previously documented. Using this technique, scientists at GRC and The Johns Hopkins Hospital gave volunteers a small dose of the radioactive element thallium during strenuous treadmill exercise. This allowed them to measure blood flow to the heart muscle. While conventional electrocardiograms given to 233 volunteers found 22 percent of those in their seventies had signs of CAD, thallium scanning added to exercise electrocardiography revealed 56 percent of the same group with the disorder, many with no other signs of heart disease.

Thirty-six volunteers who were free of CAD on stress/thallium tests were given another radioactive element, technetium 99, to measure the quantity of blood ejected with each stroke of the heart during exercise. The tests showed no age-associated reduction in pumping of blood, even during vigorous exercise.

There is a large age-related change in kidney function. On the average it diminishes by about 40 percent between 20 and 80 years of age. There were marked individual differences, however, with a progressive decline in some people and long periods of stability or even increase in others. A decrement in kidney function may decrease the rate of disposal of some drugs, and will sometimes lead to an accumulation of the drug in the body.

Age-related changes in the prostate gland cause problems for many older men. Benign prostatic hypertrophy (BPH), or enlargement of the prostate, is very common after age 60. It often has been assumed that its development might relate to unstable sexual or marital relationships, or the quantity or type of sexual activity. However, a comparison between BLSA volunteers who had surgery for BPH and men of the same ages who did not require surgery, found no important differences in amount of sexual activity, number of sexual partners, or length or stability of marriage prior to the surgery.

Aging seems to have little effect on the quality of sexual pleasure in healthy women, in spite of some decreases in sexual desire, degree of arousal and frequency of or capacity for orgasm. Although many older women volunteers who were interviewed about sexuality had some physical changes apparently related to menopause, three-fourths said they noticed little or no change in sexual satisfaction over time. Of the 156 women who were interviewed about their sexual activities and attitudes, the majority reported that menopause had either a negligible effect or in some cases a posi effect on their sexuality. About one-fo of those said they enjoyed not having to worry about menstruation or birth control. Seventy-three percent of women ages 60-79 years reported a decrease in vaginal lubrication, compared to 48 percent of women 40-59 years and 13 percent of those 20-39.

Women ages 40-59 reported sexual attitudes and activities which were much more conservative than those of younger women, and more like older women; however, this seems to reflect the times in which they grew up rather than their ages. The respondents in this interview (98 percent of those who were asked to participate) were not pre-selected for a study of sexuality and their answers probably reflect quite accurately the attitudes of other women of their ages and backgrounds.

BLSA men reported steadily declining sexual activity over most years of the life span, but they tended to maintain comparatively high or low levels of sexual activity throughout their lives. Those who had a high frequency of activity in early marriage and in the 20- to 40-year age period, maintained relatively high sexual frequency after age 40. Physical well-being was also related to sexu responsiveness.

The decline in sexual vigor with aging reported by some male volunteers is ap-

Investigator Judy Friz (left) administers a battery of memory and response time tests to NIA staff member, Stella Tuszynski.

Groups of numbers are piped into Mrs. Tuszynski's headphones, and she is required to writ down the numbers as she hears them. There will be two sets of numbers being piped in at th same time, making the test more difficult for someone who may not hear well.

NIH PHOTO 1953

parently not due to a hormone deficiency since most healthy older BLSA men produce sex hormones at levels comparable to those found in younger men. Among the oldest subjects studied—men aged 70 to 89—sex hormone levels were higher in those who maintained greater levels of sexual activity. The sperm counts in older men were about the same as those in younger men but the proportion of immature sperm increased with age.

Still other BLSA studies show changes in the immune system may contribute to the increased incidence and severity of cancer, heart and infections diseases with advancing age. Lymphocytes have a decreased ability to initiate an immune response, beginning as young as age 40. Neutrophils, cells which fight acute infection, become less efficient at ingesting bacteria with aging; however, most of the other cell functions remain intact. Many older people show very little decline in immune function and investigators want to find out why some remain relatively normal in this respect and others do not.

BLSA scientists are studying how dietary and other factors affect the immune system. They hope to develop ways to boost those immune functions that continue to perform well with aging and to find methods to enhance the immune system's ability to fight disease.

Early diagnosis of disease is often a crucial factor in whether or not it can be cured or controlled. BLSA scientists, collaborating with the World Health Organization and other institutions, are studying dermatoglyphics, hand and foot print patterns unique to each individual from before birth. Some preliminary findings show that variations in these patterns may one day help doctors detect individuals at high risk of cancer, diabetes, heart and other diseases associated with aging. So far, they have found significant dermatoglyphic differences between breast cancer patients, those at high risk of developing breast cancer and normal BLSA volunteers who were in neither of those categories.

These findings cannot be used now to predict whether or not an individual might develop breast cancer. Even though the results were dramatic, a relatively small sample of women was used and further research is necessary before this information can have practical diagnostic applications for individuals. The investigators hope that this research leads to methods which, along with other diagnostic tools, will help identify potential breast cancer patients.

Aging does not bring basic personality changes, according to BLSA volunteers. Although there are changes in attitudes and opinions with aging, the basic dimensions of personality do not change with age and are not influenced greatly by life changes among healthy individuals, say BLSA scientists. They base this evaluation on personality ratings by families and acquaintances of BLSA volunteers as well as on psychological and personality tests given to the volunteers.

When asked how they coped with a recent stressful event such as death of someone close or personal or family illness, older volunteers reported coping in much the same way as younger subjects do. When they use different ways to cope, it seems to be in response to situations more frequently found in older people, such as general loss of health.

Although loss of health is one of the biggest threats older individuals face, older volunteers did not complain more about their health than did younger persons. When they did complain, most of their problems dealt with the sensory, cardiovascular, or genitourinary systems—which are most susceptible to age-related disease and disability. Excessive health complaints among BLSA volunteers were associated with poor psychological adjustment. However, studies show that at any age, individuals who are very neurotic complain more about their health.

The ability to learn remains with healthy people through advanced old age. BLSA volunteers continue to learn into their eighties and nineties. However, older people did make more errors on experimental learning procedures than did younger persons and the age differences were more pronounced when the volunteers had less time to respond.

Visual memory showed very little impairment up to the late seventies. However, even among the oldest volunteers, there were some who did not show these changes. One of the possible reasons for age-related changes in visual memory and other functions is a decline in health. Investigators found no correlation between blood pressure and visual memory after adjusting for age and they are looking at other health factors such as the use of medications, to see if any relationship exists.

BLSA volunteer Margaret Groff, Jane Coffin's daughter, takes a test to measure static strength of shoulder and arm muscles. Margaret is the third generation of her family to participate in the aging study. The results of this test show that static strength in shoulder and arm muscles only declines slightly until after age 65 in most healthy individuals.

NIH PHOTO 1954

Aging is inevitable; however disease and disability with aging can often be avoided. By studying healthy people like Jane Coffin and the other volunteers, BLSA scientists are gradually uncovering information about the complex mechanisms underlying human aging. They hope one day to discover the reasons for functional declines with aging, to understand why certain diseases occur more frequently with advancing age and to know why women live an average of seven to eight years longer than men. Their goals are not to prolong life, but to help extend the healthy, productive middle years and to improve the quality of life for older Americans. ■

# Responsible Use of Animals in Research Discussed at Recent Symposium

Mary Donovan

Who is to decide if a particular research project is important enough to warrant the use of animals, and who determines the most appropriate animal models to use? In most cases, it should be the individual investigator, Dr. James B. Wyngaarden, NIH Director, said in his opening remarks at a recent two-day national symposium on research animal welfare.

"The Federal Government cannot on its own deal adequately with the mounting pressure concerning animal welfare," he said. "It is the reponsibility of the institutions and investigators involved to become more active in responding to questions about the need for animals in research and appropriate safeguards."

The symposium on "Imperatives in Research Animal Use: Scientific Needs and Animal Welfare" brought together some 450 biomedical researchers, laboratory animal specialists, ethicists, and public officials to discuss scientific and humane considerations in research involving animals. Participants at this meeting agreed that a committed and knowledgeable scientific community is the first and most essential step toward ensuring the appropriate and humane use of animals in research. Approximately half of all NIH-supported research projects involve animals, more than 90 percent of which are rodents.

NIH's Office for Protection from Research Risks, which planned the meeting, oversees policies and procedures to ensure that Public Health Service (PHS) award recipients who use animals in their research meet the requirements of the PHS policy.

In his keynote address, Dr. Donald Fredrickson, former NIH Director, explained that experimentation on animals is an ancient practice, more than 2000 years old, and that throughout the history of biological research, experimenters have been ambivalent about the use of animals. However, he added, thanks to more than a hundred years of heart studies with animals, we are steadily moving toward prevention of the most prevalent fatal cardiovascular diseases. In addition, he singled out the mouse as a great contributor to the advancement of modern immunology, genetics, transplantation, and cancer research.

In a panel on clinical medicine chaired by former television broadcaster John Charles Daly, Dr. Lawrence H. Cohn, Director of Cardiac Surgery Research at Brigham and Women's Hospital, Boston, described the advances in cardiac surgery since 1907 due to the use of animals in research. He was followed by Dr. Stuart W. Jamieson, Director of Cardiac Surgery Experimental Laboratories at Stanford University Medical Center, who described the important role of animals in improving results of organ transplantation. Several patients spoke, presenting dramatic stories on how animal research contributed to the development of procedures that saved their lives.

The second panel consisted of ethicists who outlined the ethical arguments for and against animal experimentation. Dr. Constance Kagan of the Animal Political Action Committee, explained that the animal protection movement includes three main groups—those concerned about animal welfare, the utilitarians and those concerned about animal rights. The three groups differ in the ways they conceptualize the status of animals and the specific human obligations to animals. What is common to all of them, she said, is a recognition that animals are objects of moral concern.

Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, greeted the symposium participants and reminded them that the "humane use of laboratory animals is a legitimate concern for the federal government. However, he added, the specific behavior of individual researchers and their host institutions is ultimately a personal decision generated by their sense of a "calling in science."

NIH PHOTO 1955

The auditorium at the National Academy of Sciences housed the two-day meeting held in April, that brought together several hundred professionals and laypeople interested in the use of animals in research. The above shows a patient with heart disease, an area of research that has benefited greatly from animal experimentation.

NIH PHOTO 1956

During the symposium, Theresa Rye, R.N. eloquently described her experience as a patient who had open heart surgery in 1982 for a rare congenital heart defect that would have eventually caused death, if left untreated. The procedure would have been impossible to perform had there not been prior experimentation with an animal model.

NIH PHOTO 1957

Dr. Arthur Caplan from the Hastings Center further described the concept of "moral stewardship," which obliges scientists to adopt a protective attitude toward the animals they use in research, based on the view that animals possess characteristics worthy of respect but that animals do not necessarily have rights. He emphasized the notion that human responsibility dictates humane behavior toward animals. He admonished researchers to realize that they cannot and should not dismiss the claims and arguments of their critics. "In a democracy, science is public business, and as such, the concerns of all interested groups must be treated seriously."

He outlined the following issues as ones that deserve consideration by the scientific community at this time: Can fewer animals be used in research and at what price in terms of safety and scientific progress? Are current regulatory guidelines and practices concerning animal welfare adequate and, if they are not, what ought to be done to modify them? Do greater efforts need to be made to educate the research community about its responsibility in using animals for research purposes? Are there new techniques or practices that can reduce or ameliorate pain in those animals that are used in research?

The second session of the symposium opened with a discussion by Dr. William F. Raub, NIH Deputy Director for Extramural Research and Training, of proposed changes in the PHS policy on animal welfare. The proposed changes are a refinement of the current policy and, in some cases, are more demanding on the institutions. They have been made to ensure that institutions receiving PHS funds appropriately use and provide care for animals involved in research. One of the changes states that institutions should designate specific lines of authority for those involved in animal care and use. A "senior" official would be named at each institution, and an animal research committee would be required to review and approve experimental protocols for the care and use of animals. Periodic inspections of the facilities would also be performed. Dr. Raub said, "This function would not duplicate or substitute for the review carried out by the NIH study sections or other peer review groups within the government."

Dr. Raub added that "We hope that the proposed refinements in the PHS policy will make it easier for everyone involved to know what is expected of him or her and yet avoid both undue restraints on scientific inquiry and unnecessary expense."

Dr. William Gay, Chief of the Animal Resources Program Branch, NIH Division of Research Resources, chaired a panel on models for developing new information in biomedicine, which, in some cases, may replace animals in research testing. He explained that the development of non-animal research models is not intended to replace the use of animals in some experiments. The nature of the scientific question being asked determines whether a non-animal or an animal model should be used. For instance, the activity of a specific hormone might be studied most efficiently in a cell culture system where extraneous materials can be eliminated or controlled. In recognizing the need to know more about non-animal models, NIH is supporting a study conducted by the National Academy of Sciences on biomedical research models, which is exploring the relevance of cell systems, lower organisms, and mathematical simulations.

Commenting on current attitudes at research institutions about the welfare of animals in research, Dr. R. W. Lamont-Havers of the Massachusetts General Hospital and former Deputy Director of NIH, added that there has been a growing recognition that the use of animals is a privilege extended by the institution to its staff and not a right to be demanded. This privilege carries with it certain obligations on the part of the institution and its staff to treat animals humanely. For instance, this includes designing meaningful experiments, using the smallest possible number of animals, having an explicit justification for using a particular species, and proving that no practical alternative method of obtaining the desired knowledge is available.

Dr. Karl Johan Obrink of the Biomedical Center, Uppsala, Sweden, ended the symposium with highlights from an international perspective. "The only way to biomedical knowledge is to study life itself," he said. "For every experiment a judgment must be made on the use of animals. Our main concern must be the attitude of the scientific community toward the animals in research rather than the formulation of laws and regulations." ■

# Strategy for Preventing Congenital Rubella Infection Discussed at International Symposium

Dr. John Burke

Scientists and physicians from around the world gathered at the Pan American Health Organization in Washington, D.C., March 13-15, for a symposium sponsored by the Fogarty International Center, (FIC), the World Health Organization, (WHO), and other groups, to discuss the prevention of congenital rubella (German measles) infection.

This symposium, the first international meeting on rubella since 1969, resolved several major scientific questions about this disease. These questions included whether the rubella vaccine confers long-term immunity; and whether the vaccine would cause birth defects if it were inadvertently administered three months before or after conception. Recommendations were also made for nations now considering rubella vaccination programs.

Rubella has been recognized for 200 years, and is usually a mild disease. However, rubella can have a devastating impact on a fetus, causing birth defects such as deafness, cataracts, cardiovascular lesions, mental retardation, generalized growth retardation, and central nervous system abnormalities. The fetus is particularly vulnerable to this virus, and it has been documented that essentially every organ can be affected. The manifestations of the infection are called congenital rubella syndrome (CRS).

In 1969, U.S. health authorities were faced with a difficult decision. An epidemic of rubella infection and congenital rubella syndrome was expected. In 1964-65, 20,000 children were born with birth defects resulting from intrauterine infection arising from rubella infection in mothers. A vaccine had recently been licensed and strategies were discussed to prevent congenital rubella infection through vaccination programs.

The essential strategic dilemma posed in 1969 resulted from limited scientific evidence. The duration of the immunity of the vaccine was not known; would immunization in childhood last long enough to offer protection to women in childbearing years? A second question concerned the safety of the vaccine administered to women of childbearing age; what would be the effect on the fetus if the vaccine were inadvertently administered to a woman not knowing she was pregnant at the time or who became pregnant within three months of vaccination?

In the limited number of countries in which rubella vaccines have been used, two different major approaches have been taken—the selective vaccination of females to provide individual protection—and universal vaccination to interrupt rubella virus transmission.

Most nations chose a strategy of vaccinating young girls in the 10-14 year age group. Countries using this selective vaccination strategy, however, experienced epidemics. There were outbreaks in the United Kingdom in 1978-79, and in 1981-82. Other nations that adopted the selective immunization protection of girls and young women have experienced similar outbreaks, with the exception of Australia, which has not had an epidemic in 14 years.

The United States elected an approach of universal immunization of young children. The result was that the chain of epidemics was broken. The incidence of rubella infection fell from an estimated 500,000 cases in 1964-65 to fewer than 1,000 cases in 1983, but more importantly the incidence of congenital rubella syndrome fell from 20,000 cases to seven reported cases of babies born in 1983 who were affected with CRS.

However, neither the universal nor selective approach has been completely augmented. The U.S. has had to immunize susceptible young women who had escaped early childhood vaccination. The United Kingdom was only recently able to vaccinate 85 percent of young women, the figure considered necessary to have an impact on the reduction of congenital rubella syndrome.

A change in strategy from selective to universal could lead to a more serious, even tragic situation. Selective immunization does not interfere with the circulation of the wild virus (occurring naturally, not by vaccination) which offers immunity to many children. Interruption of transmission of the virus raises the age of onset of the disease from childhood to the early childbearing years. Thus, changing strategy in midstream would increase the number of susceptibles in the childbearing years and most likely would increase rather than decrease the number of cases of congenital rubella syndrome.

The accumulated evidence discussed at the recent symposium demonstrated that the vaccines are not only safe, but give long-term immunity. Evidence demonstrates that the vast majority of individuals vaccinated 12 years ago continue to have protective antibodies, and other research shows rubella antibodies persisting for up to 16 or 17 years after initial vaccination. Although antibody titers decline somewhat over the years, the decline in antibody levels of naturally-infected individuals parallels those of vaccinated individuals. In the United States the RA 27/3 vaccine was shown to have a significantly better response than vaccines used earlier, and subcutaneous vaccinations were more effective than intranasal.

A second major issue resolved at the symposium was whether the vaccine would cause birth defects if administered in the time period between three months before, and three months after, conception. It has been estimated that approximately one-third of the therapeutic abortions for rubella have resulted from vaccine-associated cases. Evidence presented by the Centers for Disease Control, however, indicates that in two studies of babies born from a total of 214 women vaccinated during pregnancy, there was no evidence of congenital rubella syndrome-like defects.

A study of 91 women in Germany yielded similar results. There is a 3 percent maximum theoretical chance of CRS based on 95 percent confidence limits when women are vaccinated in pregnancy. The rubella vaccine virus strains are known to cross the placenta; however, the risk of placental or fetal infection is minimal. It was concluded that if vaccination inadvertently occurs within three months before or after conception, the risk of congenital rubella syndrome is negligible. But, because of the small theoretical risk involved, vaccination during pregnancy is still contraindicated. Australia has a policy of advising that therapeutic abortion is not necessary in vaccine-associated cases, however. As a result of the data presented at the symposium, it is anticipated that other nations will follow suit.

A report from Japan raised the question of the possible existence of rubella virus strains of varying teratogenicity (ability to cause abnormal fetal development). Pregnancies complicated by rubella virus infection were studied, and of 122 carried to term, only two babies were born with CRS. Both children suffered hearing loss, but were without other gross abnormalities.

Birth defects due to rubella often are not manifested initially. Delayed manifestations include deafness, diabetes, thyroid dysfunction, growth hormone deficiency, ocular damage, vascular effects, and progressive rubella panencephalopathy (diffuse disease of the brain). Ocular damage sometimes caused by the rubella virus may include either cataracts or glaucoma.

Rubella virus has been shown to multiply in the pancreas. A study of 241 children with congenital rubella syndrome in New York indicated that 30 had developed diabetes mellitus. One study estimated that 20 percent of juvenile autism is associated with CRS. Rubella is the only infectious disease associated with autism.

It is estimated that thirty thousand Americans have hearing impairments due to congenital rubella infection (about 14 percent of all cases of deafness) and, in American schools for the deaf, rubella is the leading cause of deafness.

In the next twenty years it is expected that rubella immunization programs in the U.S. will prevent the occurrence of about ten thousand incidences of sensorineural deafness. Calculations indicate this will save at least two billion dollars in rehabilitation and care costs.

It was suggested that the major threat to U.S. citizens who are susceptible to rubella infection comes from travel. A report was presented at the meeting that there is clear evidence from antibody studies of vaccinated and non-vaccinated adolescents that there is a "herd effect" resulting from rubella vaccination, that is, a susceptible individual is protected by virtue of belonging to a larger group of protected individuals.

Although rubella vaccines have been used extensively in some North American and European countries, they have been given only sparsely in developing countries. Requests were made at the symposium for guidelines for nations contemplating rubella vaccination programs. It was suggested that studies be carried out to ascertain the extent of CRS. It was recommended that any vaccination program be preceded by surveys to determine antibody levels and the status of immunity of the female population, particularly women of childbearing age. It was further recommended that if the immunity levels are high, for example in the 95 percent range, rubella vaccination programs should be deferred, particularly where health services are insufficient to provide for universal childhood immunization. In countries with high immune positive populations, there are expected to be regions where the immune status of individuals is low. To protect the susceptibles in these areas, vaccination was recommended.

Both strategies of universal and selective immunization present drawbacks. A less than completely successful universal vaccination program of pre-school children delays the age of onset of rubella amongst those susceptibles, and consequently can increase the risk of congenital rubella syndrome. Computer calculations indicate that a selective immunization strategy involving pre-pubertal and adolescent young women requires 70 to 80 percent coverage to have an impact on reduction of CRS. However, computer calculations also indicate that either the universal or selective strategy will be successful once one achieves 80 percent coverage of the targeted populations. A choice of strategy requires consideration of changing maternal age patterns, alterations in transmission patterns caused by socially mobile populations, and consideration of neighboring nations' rubella vaccination strategies. In Europe, various countries are adopting different strategies. Economic analysis indicates that any rubella immunization strategy that achieves the intended coverage of the target population would be cost-effective.

A major question left unresolved was the antibody level necessary for protection. Most rubella antibody testing is accomplished in the U.S. by use of commercially available reagent kits. Because of the large variety of tests available, it is not uncommon to observe variance in results by different tests. That is, one procedure can report no detectable antibody and another test show detectable antibody. Concern was repeatedly voiced about the definition of immune status in some subjects who exhibit low antibody level. Finally, it was recognized that little is known about the nature of rubella antibody as detected by different tests, and what level and nature of antibody protection is adequate during subsequent exposure to the virus.

Consequently, a major focus of discussion was the need for standardization of rubella testing and the interpretation of antibody values observed in different tests. The recommendation was made that a workshop be convened to consider adoption of international standards for testing and interpretation of results.

The symposium concluded with the recognition that much has been learned about rubella vaccination programs in the past 15 years, but much remains to be done to prevent this disease. In only a very few countries has significant progress been made toward eliminating the problem. Congenital rubella infection continues to cause tragic damage in countries throughout the world, although highly effective and safe vaccines are available. It now remains for these preventive measures to be used to the maximum advantage.

The proceedings of the symposium will be published in the *Reviews of Infectious Diseases*. For additional information, contact the International Studies Branch, Fogarty International Center, National Institutes of Health, Building 16A, Room 205, Bethesda, Maryland 20205. ■

# The Teaching Nursing Home: One Answer to the Improvement of Long-term Care

Clarissa K. Wittenberg

Getting older does not mean that disease and disability are inevitable. Personality does not appear to change significantly and the ability to learn appears to remain into the eighties and nineties. NIH PHOTO 1958

In 1982 there were 1.5 million people, the majority older, in 19,000 nursing homes at a total cost of $27 billion dollars. In 1963 only 2.5 percent of the nation's elderly were in nursing homes. Today, the number has reached 4.8 percent or 1.1 million residents 65 years and older.

It is easy to see how busy our general hospitals are, but more people, largely invisible to the general public, are in nursing homes on any given day than are in acute care hospitals. Almost one in twenty of those over 65 are in a nursing home; most are women because they live longer, are often widowed and hence, frequently isolated. However, even the highest numbers, the largest dollar figures, do not begin to trace the impact of so many people needing long-term care or the challenge faced by health care personnel in meeting such needs. Nor do they tell the human stories involved in each such placement. This situation is complicated by the fact that in a country which justifiably prides itself on the excellence of its medical care, long-term care, most frequently delivered in nursing homes, occupies a less than favorable position.

As the group known as the baby boom ages, the growing number of elderly will increase the need for medical services and long-term care. Today, there are 26 million over age 65 and by the year 2000 there will be 36 million. Demographers predict an increasing number of the elderly, particularly in the group over age 85, a phase of life which is characterized by chronic illness and heavy need for health care services. This group is expected to more than double by the end of the century, increasing to 5.4 million from about 2.6 million in 1980.

Historically the United States inherited a European long-term care system dating back to "poor houses" and "almshouses." Many factors have converged to render old style patterns unresponsive to today's needs, including longer life expectancies, relative affluence, strong family ties—but strained by geographical separation—and high technology medicine. It is clear that changes must occur, forced by social and humane reasons as well a demographic, epidemiologic and economic necessities.

Today, economists note that one out of 10 U.S. dollars is spent on health and about 30 percent of all health care spending is on behalf of older Americans who comprise 11 percent of the population. In 1983 the Health Care Financing Administration projected that U.S. health care costs reached $362 billion. There has been a pattern of continuous increase with the $322 billion figure in 1982, 12.5 percent higher than the 1981 costs. The increase in that one year period occurred three times as fast as growth in the Gross National Product.

Federal agencies, private organizations and both nonprofit and for-profit nursing home groups are cooperating to make the necessary changes so that long-term care will be equal to the challenge. A recent conference co-sponsored by the National Institute on Aging (NIA) and the Beverly Foundation, March 24-27 in Washington, D.C., brought together educators, health care personnel, nursing home administrators and researchers to discuss one such approach to the modernization of long-term care. At the conference, entitled "The Teaching Nursing Home: A New Approach to Geriatric Education, and Medical Care," an enthusiastic multidisciplinary audience listened attentively to a diverse group of speakers address the many issues involved in moving from a conventional nursing home to a program that involves research in chronic disease and service delivery, training of health care personnel in geriatrics and all the concommitant changes that accompany affiliation with academic institutions and community groups.

To trace the development of this innovative approach to long-term care, in 1981 Dr. Robert Butler, then Director of the NIA, published an article in *The Journal of the American Medical Association* calling for "teaching nursing homes." These long-term care facilities would be affiliated with medical, dental, nursing and pharmacy schools and would foster research into clinical issues such as patient management and chronic diseases. Pressing for action, Dr. Butler said, "The image of the nursing home is scarred by scandal, abuse, ignorance and fear—an image similar to that of the ancient hospital untouched by science." He noted that doctors referred patients to nursing homes, but rarely followed them after their admission. According to Dr. Butler, the growing number of elderly, the increase of chronic illness in old age, the need for long-term care, and the individual and societal cost of such care combine to make this an issue of almost unprecedented importance.

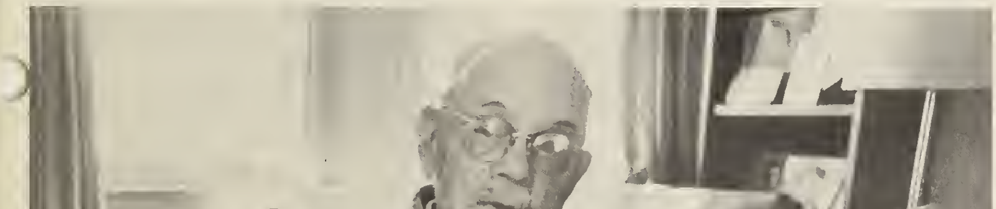
Soon after Dr. Butler's article was published, the NIA established grants to support teaching nursing home programs. The NIA currently funds six teaching nursing home programs located in Baltimore, Boston, Cleveland, New York, Philadelphia, and San Diego. Other teaching nursing home programs are being supported by the Beverly Foundation and the Robert Wood Johnson Foundation. The W. K. Kellogg Foundation has provided grants to facilitate the training of geriatric nurse practitioners so that they can play major roles in providing nursing-home care.

Each program is different, but each emphasizes some aspect of research on disease processes in the elderly, the improvement of nursing home care, the design of community and clinical strategies to prevent or postpone placement in a long-term care facility, and rehabilitation of patients and assistance after their return home. Although there is no central registry, it is estimated that there are about 20 teaching nursing home programs around the country.

Dr. T. Franklin Williams, Director of NIA, asserts that all our health care professionals should have basic training in geriatric medicine. Theoretically each university medical, nursing and dental school could be affiliated with a nursing home. Speaking at the Teaching Nursing Home Conference, Dr. Williams stated that from the 1880's in Sir William Osler's day at Johns Hopkins, an early exemplary teaching hospital, to the present, modern medical education has been based on taking the student to the patient. Osler's innovative method was reinforced by the landmark Flexner report on medical education in 1910 and has proven its value. However, in the early years of this century the focus was on the innumerable life-threatening acute illnesses.

Today, Dr. Williams notes it is the functional disorders and chronic diseases among our rapidly growing numbers of older people, and the interrelationships of these problems with the available assistance in the community that present the critical challenge. Thus "taking the student to the bedside" must be translated as taking the student to the private home, the nursing home, the retirement home and to the hospital when necessary. According to Dr. Williams, responsible medical educators will need to plan to teach geriatric medicine, and all licensing boards such as The National Board of Medical Examiners, the American Board of Internal Medicine, and the American Academy of Family Practice have already or will soon add requirements for knowledge and experience in the area of geriatrics.

Alternatives to long-term care such as adult day care and home care need to be developed. Dr. Edward L. Schneider, Associate Director of the NIA, has pointed out that "teaching nursing homes are not intended to divert attention and resources away from the development of alternatives to institutionalization." NIA has formalized this conviction in its grant description and is encouraging biomedical, social and behavioral research in a variety of home, community and institutional settings. Prevention of disease needs to be emphasized and skilled communication of information useful to individuals in maintaining their own health should be a priority, as well as a continued press for improvement in geriatric care at all levels. American progress in pediatrics has been impressive. Similarly, strides in immunology have been extraordinary with many epidemic diseases virtually wiped out. Changes in surgical techniques are nothing short of miraculous. Now these advances must be placed in the service of all our citizens to foster better health and therefore, better lives, in their later years.



Nursing homes continue to be a major source of long-term care for the elderly. Teaching nursing homes offer a more modern approach to long-term care, where research and teaching are combined to help conquer disease.

NIH PHOTO 1959

The addition of each new component to a long-term care facility—research and teaching— brings new expense, the levels of which are just being established. For example, the NIA program has given a five-year teaching nursing home grant of $2.96 million to the Albert Einstein College of Medicine and a five-year grant to a consortium of Philadelphia institutions of $4.47 million. It is calculated that these will be cost-effective expenditures as a great deal will be learned about chronic disease which may eventually curtail the need for long-term care.

Consider, for instance, the gain to be made in the area of Alzheimer's disease. There are from two to three million Americans with Alzheimer's disease and at least one million so severely afflicted as to require long-term care. Teaching nursing homes could help to conquer this disease by bringing such patients to the forefront of research and medical care. Customarily these patients are not found in acute-care hospitals, nor are they currently housed as they once were in mental hospitals, but rather they are found in nursing homes. Research on this disease, a priority area for NIA is proceeding at a promising rate. If all of these factors could begin to reduce the nursing home population by 10 percent the gain would be a savings of over $2 billion a year.

Training of physicians and other health service personnel and the costs of care of the indigent have historically been part of the cost of medical care in our large teaching institutions. This problem will eventually have to be squarely faced in innovative long-term care facilities such as the teaching nursing homes. In an era of budgetary restraints, adding any costs to those of basic care will demand careful justification. Since the costs of care for so many chronically ill patients are paid by Federal funds, a policy decision will have to be made to absorb these extra-care costs such as research and training into regular fees or whether added expenses will have to come, as now, from special grants.

The lesson of teaching hospitals would advise that these new long-term care programs will be too valuable to discontinue and that financial planning to finance key model units be commenced. Dissemination of results from these model programs could then be accomplished via a consortium of agencies and organizations as suggested by Dr. Williams at the recent teaching nursing home conference, as well as via the usual mechanisms for sharing research. There is little doubt that long-term care in this country needs to undergo change. The teaching nursing home concept has been enthusiastically embraced and is evolving rapidly and must be viewed optimistically for its potential benefit. ■

# Study Shows Lowering Cholesterol Can Reduce Chances of Heart Attack

Prepared By
The National Heart, Lung,
and Blood Institute

For the first time, a clinical trial has demonstrated conclusively that lowering elevated blood cholesterol can also reduce an individual's chances of incurring a heart attack. That finding was announced recently when the National Heart, Lung, and Blood Institute (NHLBI) released the results of its 10-year Lipid Research Clinics' Coronary Primary Prevention Trial (CPPT).

Furthermore, the investigators noted, the reduction in incidence in coronary heart disease was related to the degree of cholesterol-lowering obtained, and the greater the reduction in cholesterol, the greater the reduction in heart disease. The relationship was a one-to-two ratio: participants who reduced total cholesterol by 25 percent reduced their risk of heart attack by 50 percent.

The CPPT, a double-blind study, was designed to test the efficacy of reducing blood cholesterol levels in middle-aged men who were asymptomatic, but were considered at high risk of heart attack because of primary hypercholesterolemia (type II hyperlipoproteinemia). Of more than 480,000 men initially screened, a total of 3,806 were selected to participate in the study conducted at 12 Lipid Research Clinics in the U.S. and Canada. Men were recruited who were 35 to 59 years of age at entry into the trial and whose plasma cholesterol was 265 mg/dl or higher—markedly elevated levels.

Volunteers were not accepted who had type III hyperlipoproteinemia or evidence of heart disease, such as angina pectoris, history of myocardial infarction, congestive heart failure, or a variety of ECG abnormalities indicating heart block, ventricular hypertrophy or premature ventricular contractions. Men were also excluded who had hypertension or were taking antihypertensive medications or were found to have coexistent conditions such as cancer. Women were not enrolled into the study because, with their substantially lower risk of coronary heart disease than men, a very much larger study would have been necessary to achieve statistically significant results.

Participants in the study were randomly assigned into one of two groups, which were similar in most of the variables measured, including number of cigarettes smoked per day, blood pressure, and mean age. All the participants were placed on a moderate cholesterol-lowering diet. In addition, the men in one group were given cholestyramine at a dosage of 24 grams/day divided into two to four equal doses. The second group received an equivalent amount of a placebo dispensed in identical sealed packets.

Cholestyramine was selected for use because it can substantially lower blood cholesterol, and has been approved by the FDA for this purpose; it is nontoxic and has few side effects; and a suitable placebo is available. Both the drug and the placebo were dispensed in packets to be mixed with water or fruit juice. The participants were asked to visit the clinics every two months to renew their supply of the drug and to receive nutrition counseling and undergo a brief medical examination.

Participants were followed for a minimum of seven years and some had been enrolled for up to ten years.

The cholestyramine group experienced 155 fatal or nonfatal heart attacks during the trial and the placebo group had 187, a reduction of 19 percent. When the investigators considered only deaths from coronary heart disease, they found that 30 such deaths occurred in the drug group and 38 in the placebo group, a 24 percent reduction.

In other categories, compared to the placebo group, the group taking cholestyramine had a 19 percent reduction in nonfatal myocardial infarctions; a 25 percent reduction in risk of developing a positive exercise electrocardiogram; 21 percent fewer coronary artery bypass surgical procedures; and a 20 percent lower incidence of developing angina.

At the time the trial was initiated, the researchers anticipated that the prescribed diet would lower blood cholesterol by 4 percent and the drug would provide an additional 24 percent decline in blood cholesterol level. At the conclusion of the trial, although the difference in cholesterol levels between the two groups was statistically significant, reduction in the levels was less than anticipated. Part of the explanation for that lies in the fact that adherence to therapy was not optimal. Of a total of six packets of medication prescribed per day, the cholestyramine group was consuming an average of 4.1 packets by the end of the trial, and 72 percent of the group were not taking the drug at all. The reduced intake was partially the result of gastrointestinal side effects experienced by a high percentage of the participants at the beginning of the study.

However, the investigators noted, of the subgroup of participants that maintained a full dosage regimen for the duration of the study, the fall of cholesterol level and the drop in coronary heart disease risk clearly were related to the dose of the drug. With a full dose of the drug, cholesterol levels fell an average of 19 percent and coronary heart disease risk declined by 40 percent.

Collectively, the 3,806 men who were followed in the study made 193,000 clinical visits, generated more than a million data forms, gave 341,000 blood samples, and 72,000 electrocardiograms. Many of the participants traveled as far as 100 miles for clinic visits, and all fasted for 12 hours prior to having blood drawn and frequently filled out long and detailed questionnaires. In addition, none of the men was aware of which group he was in, nor were any of the physicians unblinded, and no one was permitted to know the results of their blood studies. Thus, the participants did not know until the conclusion of the trial whether their persistence was being rewarded with improvements in lowering cholesterol levels.

Although the participants in the trial were middle-aged men, the investigators recommended that the results can be extended to younger men with elevated blood cholesterol, to women with high cholesterol levels and to individuals with more modest elevations in blood cholesterol, namely above 240 mg/dl. It is emphasized that the first step in lowering blood cholesterol is always dietary. ■

# Further Developments Made in Artificial Skin

Doris Brody

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Burn injury is the third leading cause of accidental death in the United States. Seventy five thousand people are hospitalized with severe burns annually; 12,000 die. One-third of these burn victims are children under the age of 15.

To help reduce this toll, speed recovery, and lessen disability and disfigurement, the National Institute of General Medical Sciences (NIGMS) supports research which aims to improve our understanding of the fundamental physiological mechanisms underlying the complications of burn injury. Although NIGMS is especially interested in basic studies on the molecular, biochemical, and physiological changes caused by burns and trauma, research results are often translated into improved patient care quite quickly.

A case in point is the development of an artificial skin by NIGMS-supported scientists Dr. Ionnis Yannas of the Massachusetts Institute of Technology in Cambridge and Dr. John Burke of Massachusetts General Hospital in Boston.

Rapid wound closure is very important for burn or trauma victims since open wounds lead to serious fluid losses and greatly increase the risk of life-threatening infections. At present, wounds in which extensive areas of skin have been destroyed cannot be closed without the use of grafts. The only grafts that "take" permanently are from the patient's own skin and, unfortunately, this may be in short supply. When this happens, temporary coverings, often grafts of pig or cadaver skin, are used to cover the wound. To slow the rejection which ultimately occurs with these grafts, immunosuppressant drugs must be given. These, in turn, lower the patient's resistance to infection. The temporary grafts must also be removed when the permanent graft is applied, thus subjecting the patient to another surgical procedure.

The artificial skin promises to avoid many of these problems. Drs. Burke and Yannas have successfully tested the material on 40 severely burned patients ranging from the very young to the elderly. They found the skin, which is composed of interlaced fibers constructed from cowhide collagen (a major protein of connective tissue) and shark cartilage, to be a good wound covering. It does not cause infection, inflammation, or rejection, and it cuts healing time significantly because, although the top layer must be removed and the wound closed by thin mesh grafts of the patient's own skin, it is not necessary to obtain full-thickness grafts from the patient.

This "stage 1" artificial skin is now being developed by a commercial laboratory and has received FDA approval to be tested in selected burn centers across the country. Within the next year or so, the material should become available for widespread use in treating severely burned patients.

However, the scientists' ultimate goal is to develop an artificial skin that will not require any grafting of the patient's skin. Their "stage 2" skin, which they have tested on guinea pigs, is a step in this direction.

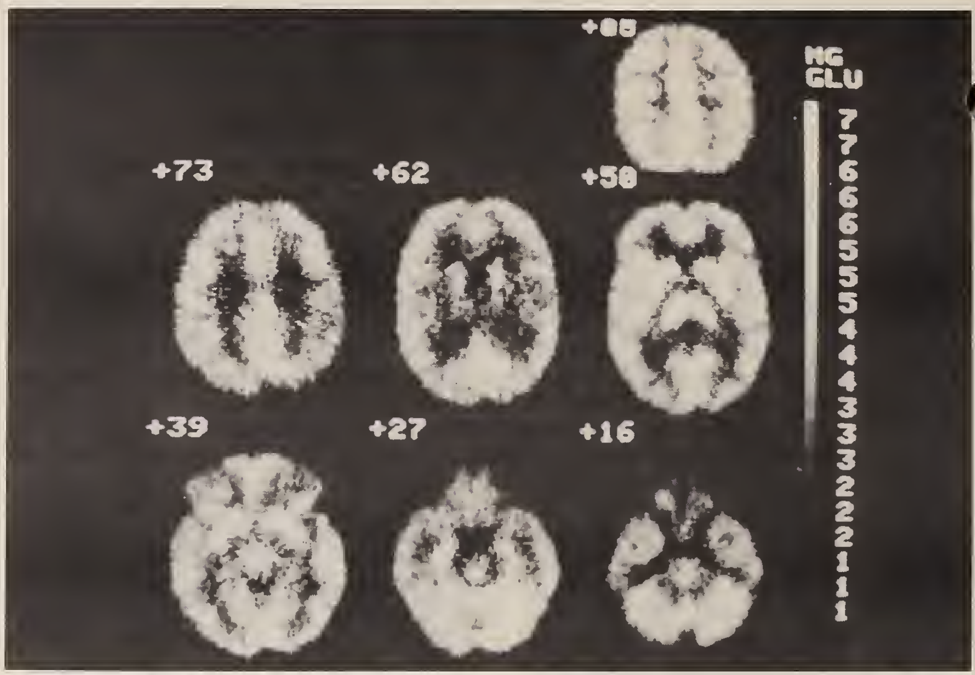
In both stages the artificial skin consists of two layers. The top layer is made of silicone, which can be peeled off quite easily. The bottom layer is constructed of highly porous fibers of collagen that are specially designed to serve as a template for the regrowth of the patient's dermal or inner skin layer. In stage 2, the artificial skin is seeded with a small number of the recipient's own epidermal (outer layer of skin) cells which will grow to cover the new dermis, forming a complete new skin.

In guinea pig trials with the stage 2 skin, healing with new full-thickness skin took place in only 14 days. Although the new skin seemed functional, it contained no sweat glands or hair follicles.

The researchers are now working to define more precisely the properties and structure of the regenerated guinea pig skin. They also need to determine the ideal density of the epidermal cells that are used to seed the skin before this stage 2 artificial skin will be ready for clinical trials with burn patients. ■

# How PET Works—Subject at Recent Science Writers' Seminar

Bobbi Bennett



Pictured here are seven horizontal parallel slices of the brain of a normal individual. From top (upper right) to bottom (lower right), these images were taken simultaneousy in 10 minutes with an NIH-developed high resolution device called the Neuro-PET. FDG, a positron-emitting glucose-like analogue that acts as a tracer was intravenously administered to the individual so that the physician can see the functional anatomy of the various segments of the brain. Observing these "pictures" the researcher can "see" the areas of the brain that consume less amounts of sugar than other areas (black area), and the white areas are high in glucose metabolism.

NIH PHOTO 1960

If the business of the body is conducted with the coin of chemicals, to borrow an image from the Clinical Center's Dr. Steven Larson, then positron emission tomography (PET) is one of the most exciting "financial indicators" that a researcher can use.

How PET works and how intramural scientists are using it to study patients with brain tumors, Down syndrome, and Alzheimer's disease were the subjects of a recent NIH Science Writers' Seminar.

PET's unique value, according to the moderator, Dr. Thomas Chase, lies in the fact that PET allows us to look not only at the structure but also at the function of the living brain. Dr. Chase is Chief of the Experimental Therapeutics Branch of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Dr. Larson, Chief of the Clinical Center's Nuclear Medicine Department explained the underlying principles of PET. The diagnostic imaging technique involves the injection of a radiolabelled chemical—a positron emitter—into a vein in the patient's body. Positron-emitters are some of the most biologically abundant elements of carbon ($^{11}C$), oxygen ($^{15}O$), and nitrogen ($^{13}N$), as well as other conveniently reactive chemicals such as fluorine ($^{18}F$). Using these elements, one can label hundreds of chemicals of biologic importance. This is one of the great powers of PET, according to Dr. Larson.

The PET scanner consists of a series of detectors positioned around the patient's head to collect the radiation given off by these isotopes with short half-lives. Using a computer, the instrument translates the radioactive density into a map of the distribution of the radioactivity. The development of the mathematical models that convert the map of this distribution for a given biological molecule into an estimate of its metabolism by the body is based upon the fundamental studies of Dr. Louis Sokoloff, Chief, Laboratory of Cerebral Metabolism, National Institute of Mental Health (NIMH). He and his colleagues have developed the best working mathematical models for calculating the regional metabolic rate of glucose in the brain. This method—in which $^{18}F$- deoxyglucose (FDG) is used as a tracer—is now being used by virtually all major PET centers and is the standard for calculating cerebral glucose metabolism in healthy individuals and in those with various diseases.

Dr. Larson believes that PET has ushered in a new era in diagnostic imaging and that, in the future, this non-invasive technique will revolutionize our understanding of the internal chemical environment of living human tissues.

Dr. Paul Kornblith, Chief, Surgical Neurology Branch, NINCDS, described his laboratory's use of PET and FDG to study primary brain tumors. This research was done using a high resolution-high sensitivity scanner developed and built in his laboratory by Drs. Giovanni Di Chiro, Rodney Brooks, and Victor Sank. Neuro-PET, as it is known, has markedly improved the technical quality of PET studies by giving clearer, more precise pictures.

Dr. Kornblith's studies of more than 150 patients with central nervous system tumors have shown, both clinically and at the cellular level, that there is a strong correlation between the degree of malignancy and the rate of glucose utilization, i.e., the more malignant a tumor is, the higher the metabolic activity. Thus, PET may be used as a reliable method to grade primary brain tumors.

Other benefits of this method are the possibility of an early recognition of tumor recurrence and/or grade change, and the ability to differentiate between tissue destroyed by radiation with its low glucose utilization and a recurrent tumor with its increased utilization. This technique is invaluable for monitoring the effectiveness of therapy. "If a hypermetabolic area becomes hypometabolic, then there is a strong suggestion that the therapy is working. CAT scanning cannot always make this distinction," Dr. Kornblith said.

Thus, PET gives scientists an idea whether the post-operative changes that occur are related to the recurrence of brain tumors or to other causes. The PET-FDG method has opened a new chapter on the study of brain tumors since it is now possible to study the secondary metabolic effects that brain tumors may have in adjacent or even remote areas of the brain, which, at least in part, may be related to the interruption of nerve impulses to the brain.

Dr. Kornblith stressed that PET is still a research tool for brain tumors because of the complexity of issues and logistics involved. He stated that CAT scanning is the clinical tool now, but PET scanning is the direction for the future.

PET scanning is also being used by Dr. Neal Cutler, Chief, Section on Brain Aging and Dementia, Laboratory of Neurosciences, National Institute on Aging (NIA), to study brain metabolism in normal aging, Alzheimer's disease, and Down syndrome.

Studies by Dr. Cutler and his colleagues found no significant age-related changes in brain metabolism in 40 healthy men, ranging in age from 21 to 83 years. Since there is an excess of nerve cells in the young brain and a loss of neurons as an individual ages, Dr. Cutler suggests that their findings may be due to the adaptability of the nervous system, in the absence of cerebral disease, to compensate for this neuronal loss.

In preliminary studies of 12 patients with presumptive Alzheimer's disease, the researchers found minimal changes in brain metabolism in mildly demented patients but more consistent significant metabolic reductions throughout the brain of the severely demented patients. Dr. Cutler plans to study more patients with the diagnosis of dementia of the Alzheimer's type and later to confirm their diagnoses through neuropathological findings.

Dementia also occurs in about 30 percent of Down syndrome patients who are over 35 years of age. The brains of these older patients show the same pathological changes in the same regions of the brain as those seen in Alzheimer's patients. PET scans of a 51-year-old male with Down syndrome who did not have dementia, according to Dr. Cutler, showed the same metabolic rate as that of healthy age-matched men. However, PET scans of four young Down syndrome individuals (mean age 22.5 years) showed their brain metabolism to be as much as 40 percent higher than that of healthy men in their age group.

Dr. Cutler pointed out that more studies need to be done to examine the relationship among dementia, brain metabolism, and neuropathology in Down syndrome.

Other information concerning Alzheimer's disease was reported by Dr. Thomas Chase. Using PET, he and his colleagues found that the overall cerebral glucose metabolism in 20 patients with Alzheimer's disease averaged 28 percent lower than that in eight healthy age-matched individuals.

This reduction was substantially less severe in the frontal lobes than in the more posterior areas of the cortex. The posterior parietal lobes and the contiguous portions of the posterior temporal and anterior occipital lobes were most severely affected. The parietal-temporal areas of the brain are where the auditory, visual, and tactile-sensory inputs are all integrated.

Dr. Chase said, "We feel that it is this integrative function which bears the brunt of the damage in Alzheimer's, contrary to what has always been thought to be true in this disease." In their PET studies, the frontal cortex is relatively spared, but the degree of sparing gets less as the disease progresses.

They also found that the distribution of the major metabolic abnormalities identified by PET correlated with each patient's major cognitive deficits. "In fact," Dr. Chase said, "we can almost predict where the major metabolic defect will be based on the major clinical symptoms of the dementia."

Other biochemical studies of Alzheimer's patients have emphasized abnormalities of the two neuronal systems that liberate the neurotransmitters, acetylcholine and somatostatin. However, the new data indicate that these abnormalities do not fully explain the dementia of Alzheimer's since both of these chemicals are distributed more or less uniformly throughout the cerebral cortex and their reduction in Alzheimer patients is similarly distributed. Dr. Chase suggests that there may be another neurotransmitter—perhaps still undiscovered—that may be involved and that may have more direct implications for the dementia seen in Alzheimer's patients. More anatomically focused, biochemical studies will be necessary to determine which, if any, single neurotransmitter serves as the critical determinant for the functional abnormalities in Alzheimer's disease. ■

Dr. Rodney Brooks of NINCDS, explains the function of the Neuro PET-scanner to reporters at the Science Writers' Seminar on Positron Emission Tomography (PET). He was one of the members of the team who helped develop the Neuro-PET.

NIH PHOTO 1961

Dr. Thomas Chase (center) Chief of the NINCDS Experimental Therapeutics Branch, demonstrates the use of the neuro-PET scanner.

NIH PHOTO 1962

# Continued Research Urged at International Meeting on Yaws

Dr. John Burke

Yaws, a non-venereal bacterial infection, is once again resurging in areas of West Africa after two decades of control.

Members of the NIH Fogarty International Center (FIC), the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and scientists from 25 nations recently met in Washington to discuss endemic treponematoses, which includes yaws, endemic syphilis and pinta.

Yaws is found in underdeveloped, humid tropical areas, pinta is confined to small areas of Latin America and the Caribbean, and endemic syphilis is found in cooler, drier climates. Transmission is through direct contact or indirectly, as in endemic syphilis, by the use of common eating and drinking utensils. Symptoms vary from skin lesions to gross destruction of tissue and bone.

In the 1950s and 60s major campaigns were launched against yaws using penicillin, which cured approximately 46 million persons, mostly children from the poorest and most remote areas of the world.

It is currently estimated that over a million people are afflicted with yaws. The resurgence of this disfiguring and disabling disease is due partly to discontinuance of mass surveillance and to changes in health care priorities. The actual number of cases is not clearly known because many afflicted nations do not report cases to WHO on the recent incidence of yaws.

At present, investigators are unable to culture or differentiate the treponemes responsible for yaws, pinta and endemic syphilis. Evidence presented at the meeting indicates that penicillin is as effective as ever in treating endemic treponematoses; but as clinical experience has shown, some antibiotics become resistant after decades of exquisite sensitivity. For example, the related spirochete *T. pallidum*, which causes venereal syphilis, has recently developed resistance to erythromycin, a "back-up" antibiotic against the nonvenereal treponematoses.

It is not known whether yaws, pinta and endemic syphilis or venereal syphilis are caused by different treponeme species, or different strains within the same species or subspecies.

Within the last four years, remarkable advances in molecular biology have made the solution to these questions possible. It was also reported at the symposium that the prospects for new diagnostic tests are good; and that monoclonal antibodies certainly have the potential to differentiate and identify the subtle antigenic diversity that may exist among strains or subspecies of the pathogenic treponemes.

DNA homology studies and the use of polyacrylamide gels have led to the identification of many protein antigens that are shared by the various species of treponemes. It has been demonstrated that *t. pallidum, t. pertenue* (which causes yaws) and non-pathogenic treponemes are all genetically-related. DNA sequencing of *T. pallidum* has been used by investigators in the Netherlands and in Denmark to identify peptides that will be tested as potential immunogens and for diagnostic reagents. It was suggested that inexpensive serologic tests that can differentiate active yaws from late non-infectious cases in the field would be useful during selective treatment and post-campaign surveillance programs. It was also pointed out that this may be particularly important where the identification of spirochetes in lesions may be more useful than surveying antibody titers which are so often ubiquitously high in endemic areas.

A vaccine against yaws could offer the best hope for control if penicillin-resistant treponemes emerge in the future. However, prospects for a vaccine are far on the horizon. Evidence reported at the symposium strongly suggests that multiple vaccinations might be necessary to maintain effective immunity against infection with *T. pallidum*.

The question was raised whether immunity to pinta would produce an immunity to yaws or to venereal syphilis. The information presented was largely anecdotal. The antigenic similarity among *t. pallidum, t. pertenue* and other treponemes suggests that infection with one strain may provide significant protection against other treponemal infections. However, one report indicated that this cross-species protection might not be reciprocal.

Research indicates that the endemic treponematoses are found with increasing frequency in a mild, early form, or in the early latent phase. The severe distinctive lesions of the latter stages of the diseases are now less frequently observed. It was suggested that the widespread use of antibiotics may be responsible. One of the main problems is failure to recognize the disease because of inadequate experience and education, and it was recommended that attention be devoted to this problem.

This young boy suffers from yaws, a chronic, non-venereal bacterial infection, that afflicts the populations in West Africa, the Caribbean and South America.

NIH PHOTO 1963

The symposium members recommended that when the prevalence of clinical cases is greater than ten percent, then the entire population should be given a single injection of long-lasting benzathine penicillin G. When five to ten percent of the population suffers from the disease, then all children as well as patients and their contacts should be treated. When a smaller percentage (less than five percent) of the population is afflicted, then both the patients and their domestic contacts should be treated. Alternate methods of treatment for those who are allergic to penicillin should be evaluated.

Innovative control approaches were reported, for example, in Ghana where control has been combined with vaccinations against yellow fever, measles, tetanus, and tuberculosis. It was suggested that when yaws & other endemic treponematoses reach a low enough disease level, resurveys, surveillance and maintenance activities should be integrated into the existing health care system.

It was agreed that the endemic treponematoses can be brought under complete control, but what is needed is the firm commitment of the governments of the affected countries and the assistance of other nations and international organizations. Control methods should be tailored to the needs of individual countries based on results of an assessment of non-venereal treponematoses disease level, as well as an examination of the capability of the primary health care system.

The proceedings of the symposium will be published in a later edition of *Reviews of Infectious Diseases*. For further information, please write to the International Studies Branch, FIC, National Institutes of Health, Building 16A, Room 205, Bethesda, Maryland 20205. ■

# NIH Conference Recommends Long-term Drug Treatment for Depressive Disorders

Marilyn Sargent

"Individuals with recurrent mood disorders can spend up to 20 percent of their adult lives in depressive or manic episodes. The personal suffering and economic loss is enormous," said Dr. David Kupfer, Panel Chairman, at the National Institute of Mental Health (NIMH)/NIH Consensus Development conference on the use of long-term, preventive drug treatment for affective disorders.

Kupfer, Chairman of the Department of Psychiatry at the University of Pittsburgh, and 12 other panelists—mental health specialists, internists, and citizen advocates—recommended that individuals whose lives are disrupted by recurrent episodes of major depression, mania, or manic/depressive illness receive long-term, preventive drug treatment.

Their statement of consensus was based on research reports by 17 experts on mood disorders, who came from Denmark, Switzerland, Scotland, Canada, and the United States to attend the conference.

The panelists recommended that lithium be used to prevent recurrent bouts of mania or manic/depressive disorder and that lithium or tricyclic antidepressants such as imipramine and amitriptyline be used for recurrent major depression. Since most patients with recurrent major depression will have been treated previously with tricyclic drugs for their depressive episodes, "it is usually most appropriate to continue with the same drug, provided it has been effective and is well tolerated." Lithium may be preferable in patients whose past history is uncertain, since some patients diagnosed as unipolar depressives (depression without manic episodes) ultimately may develop a manic episode.

The panelists emphasized that patients who have a bipolar disorder (manic episodes with or without depression) are at high risk for recurrences of this disorder. Manic episodes are very disruptive and the likelihood of becoming psychotic when manic is great. Therefore, the occurrence of a manic episode should *always* raise the question of preventive therapy.

Unipolar disorder is less frequently recurrent than the bipolar disorder and the efficacy of the preventive treatments less clearly established. Thus, the decision as to whether and when to initiate preventive therapy is based more upon factors with individual patients. A major factor is the risk of an early recurrence. This risk is increased by the presence of concurrent nonaffective mental disorder, a chronic medical disorder, chronic symptoms of depression, and the occurrence of the first episode at an older age. Psychotic features, serious suicide attempts, or serious functional impairment during recent episodes predict increasingly severe episodes as does a family history of suicide, bipolar disorder, or psychotic affective episodes.

On the other hand, unipolar patients who have a rapid response to treatment with long intervals between episodes should not be considered as suitable candidates for preventive treatment.

Other highlights from the consensus statement were:

- Recurrent mood disorders are currently underdiagnosed and undertreated. Bipolar disorder is estimated to occur in one percent of the population. Although there are little hard data on the prevalence of recurrent major depression, recent research, such as the NIMH Collaborative Study on the Psychobiology of Depression involving five university medical centers, indicates that major depression is a more recurrent and chronic illness than was previously realized. Among patients treated at these centers, 60–80 percent experience recurrent episodes of major depression, most suffering relapse within four months. Further, 15–20 percent of these patients never fully recover from any given episode.
- Lithium reduces the incidence of recurrence and alleviates symptoms for both mania and depressive cycles in most bipolar patients. However, rapid-cyclers (patients who have three or more episodes a year) often respond poorly. The antiepileptic drug, carbamazepine, has proven effective for some patients who respond poorly to lithium, but its long-term use requires further study. Where lithium does not alleviate depressive cycles in bipolar patients, *low* doses of antidepressants may be useful but must be given under close monitoring as they may induce rapid-cycling in some patients.
- Studies have found lithium and the tricyclics to be equally effective for preventing unipolar depressions, but have provided few guidelines as to which patients respond best on which drugs. Results from the NIMH Collaborative Study of Long-term Maintenance Drug Therapy in Recurrent Affective Disorders suggest that patients with severe previous episodes have a better response to imipramine and that patients with only moderately intense episodes respond equally well to lithium and the tricyclics.

  In cases where neither lithium nor tricyclic drugs are affective, monoamine oxidase inhibitors may prove useful. Electroconvulsive therapy has helped both unipolar and bipolar patients who have not responded to other treatments.
- A major problem with long-term drug therapy is noncompliance by patients, particularly those with bipolar disorder who dislike giving up the "highs" associated with manic episodes. Patients also tend to discontinue treatment when they feel better or if they cannot tolerate side effects. Lithium may reduce energy, sexuality, and enthusiasm and can cause weight gain, thirst, fine hand tremor and cognitive problems. The tricyclics may also produce weight increase and, occasionally, cognitive problems. Psychotherapy may be a useful adjunct to treatment.
- To avoid lithium poisoning, patients should have blood levels checked at intervals of one to three months. Long-term lithium treatment poses few dangers to patients who are carefully monitored. Special caution should be exercised with the elderly, those with preexisting somatic disorders, patients experiencing severe physiological stress, and pregnant women.
- Duration of treatment depends on individual factors including the previous pattern of episodes, degree of impairment and adverse consequences associated with recurrences, and the ability of the patient to tolerate the drug. Discontinuance of tricyclics should be gradual but lithium can be either abruptly or gradually stopped. Neither type of medication is addictive or prone to abuse.

A full text of the consensus statement is availble from Myrle Kahn, 443-4536. ■

# MEETING HIGHLIGHTS

The following research advances represent highlights of studies performed by NIH investigators and presented at two scientific meetings held this spring.

The American Society of Clinical Oncology meetings were held in Toronto, Ontario, Canada, May 6-8. NCI-supported work ranged from recent advances in lung cancer to the use of interferon in T-cell lymphomas. The ASCO meetings draw scientists from around the world to present the latest advances in cancer research.

The annual International Association for Dental Research (IADR) was held March 15-18 in Dallas, Texas, where National Institute of Dental Research (NIDR) investigators presented their findings which will appear in the *Journal of Dental Research,* a publication of the American Association for Dental Research.

## Recombinant Leukocyte A Interferon Shows Promise in Treating Advanced T-cell Lymphomas

Francis X. Mahaney, Jr.

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High doses of pure human interferon have been found to be effective in patients with cutaneous T-cell lymphomas, scientists from the National Cancer Institute (NCI) reported.

Dr. Paul A. Bunn, Jr., presented findings of 20 patients with advanced lymphomas of the skin. Nine of the patients improved dramatically when given high-dose intramuscular injections of recombinant leukocyte A interferon.

The twenty patients were men and women between the ages of 41 and 72 and all were diagnosed as having advanced stages of the disease.

Dr. Bunn said that "these patients had failed known standard therapies." However, when given human interferon three times a week, the skin sores and tumors began to shrink within a month after the first treatment. Bunn also stated that the patients' cancer did not completely disappear, but that half of the group experienced a 50 percent response to the treatment. And, despite aggressive tendencies of the disease to spread to other parts of the body, these "partial responders" were found to have tumor regression lasting an average of more than five months and in some cases, more than 22 months.

In addition, five patients (18 percent) showed some improvement by the end of treatment and six patients did not respond to the treatment at all.

"We found that the activity of human leukocyte A interferon was higher than that reported for any standard or experimentally tested agent in patients with advanced cutaneous T-cell lymphoma, including drug combinations, monoclonal antibodies, deoxycoformycin or retinoic acid," said Dr. Bunn. He believes that pure human interferon should be tested on patients with earlier forms of the disease, either alone or in a combination with other existing therapies.

In a related study, NCI's Clinical Investigation Section Head, Dr. Kenneth Foon, reported that high concentrations of recombinant leukocyte A interferon were also shown to be highly effective in patients with nodular non-Hodgkin's lymphomas, that affect the B cell rather than the T cell.

He said that the B-cell non-Hodgkin's patients appeared to be equally or even more responsive than patients with cutaneous T-cell lymphoma when identical amounts of interferon were given. Four of 24 patients (17 percent) responded completely, showing no evidence of their tumors 6-12 months after treatment.

"While these four patients are not cured, the outward manifestations of their disease have disappeared and that is certainly promising," Dr. Foon said.

Among the 24 patients, nine (38 percent) showed partial response. Seven showed no response or a minimum response to interferon and in three patients, their cancers progressed. All of these patients had been previously treated with chemotherapy.

Both Drs. Bunn and Foon cautioned that the findings do not necessarily mean that a cure or a means to prevent the disease will be forthcoming, and that the two studies are only in Phase II clinical trials, an early stage of clinical research.

In both studies, the researchers said all patients experienced side effects from the interferon, including flu-like symptoms with fevers, severe weight loss, depression, and general fatigue. When interferon was reduced by half, the symptoms disappeared, Dr. Bunn said. "Even more intriguing was the response of patients placed back on the original dose again of interferon after their doses had been reduced because of side effects. Often the flu-like syndrome either did not return or was less than before."

Some of the patients tested on interferon had mild abnormalities of liver and kidney function, but these conditions abated and reversed when treatment was stopped.

Drs. Foon and Bunn said that interferon's side effects were very different from other standard drug treatments for cancer. Chemotherapy can cause such side effects as, bone marrow suppression, kidney and liver toxicity, hair loss, and even later leukemias in some patients.

The most profound side effects of the interferon treatment appeared to be weakness, fatigue and fever, but the patients seemed to adapt well. ■

# Recent Advances in Lung Cancer May Improve Future Treatment

Prepared By The National
Cancer Institute

Even though the best available treatment for lung cancer in the United States can achieve long-term survival for only 12 percent of patients, National Cancer Institute (NCI) researchers believe there is reason to be optimistic about future treatment of this disease.

Dr. John D. Minna, Head, NCI-Navy Medical Oncology Branch, said his optimism is based on "remarkable" laboratory findings about the cellular and molecular biology of lung cancer, findings that he believes will "ultimately be of clinical benefit."

A major advance, he said, has been the establishment of human lung cancer cell lines. Others include work with tumor "markers" and monoclonal antibodies to type lung cancer cells, determination of some of the growth factor requirements of human lung cancer cells, identification of certain oncogenes in some of these cancers, and early studies to test sensitivity of human lung cancer cells to drugs and irradiation.

Dr. Minna stated that more than 80 percent of human small cell lung cancers, 60 percent of adenocarcinomas and large cell carcinomas, and 40 percent of squamous cell lung cancers can be made to grow in culture. "These lines retain the tissue and biochemical properties of the patients' cancers," despite replication in cell culture for many years and despite serial transplantation in some strains of mice. Dr. Minna also said that "the cell lines seem able to generate diverse, heterogeneous cell populations much like those seen in human cancers."

To provide the most effective treatment, it is important to ascertain the exact type of a patient's lung cancer. This may be difficult to do, because lung cancer cell populations can be diverse and overlapping. Using the cell lines, investigators have so far been able to define markers that distinguish small cell from non-small cell lung cancer, (NSCLC) and small cell lung cancer (SCLC) from a variant form called SCLC-V, Dr. Minna said.

Small cell, or oat cell, lung cancer accounts for about a quarter of all lung cancers. The other types—large cell, squamous cell, and adenocarcinoma—account for about 25 percent each, or 75 percent. They are collectively called non-small cell lung cancers.

The small cell cancers are usually not operable because they grow very quickly and are usually far advanced at the time of diagnosis. This group of cancers, though, is the only type in which survival can be regularly prolonged with drugs. About 10 to 20 percent of the non-small cell cancers can be treated with surgery, with long-term survival in about half of cases. If the cancers are inoperable, only about 3 percent of those patients can be saved with irradiation.

Lung cancer cells from patient samples are also being typed with monoclonal antibodies, he continued. So far, these have been found to distinguish between SCLC and NSCLC cells. One investigator has found also that some monoclonal antibodies can inhibit cloning of lung cancer cells *in vitro* and in rodent grafts. "These applications of monoclonal antibodies need to be tested in Phase I and II clinical trials," said Dr. Minna.

The cell lines have also enabled researchers to identify some of the hormones, peptides, and growth factors that regulate the *in vitro* growth of these cells. He said that a number of the substances needed for growth have been found for both SCLC and NSCLC, but that squamous cell carcinomas are still difficult to grow in culture. Even if these studies fail to help select clinical treatment, they may yield information that ultimately will lead to treatment advances, such as blocking hormonal stimulation of lung cancer growth," he said.

Investigators have identified activated forms of some oncogenes in up to 15 percent of lung cancers. These include a point mutation in the activated *ras* oncogene, affecting one of two amino acids, that appear to cause the protein coded for by the gene to be abnormal. Another type of change entails increases in the number of copies of the *myc* oncogene, a process termed amplification, which causes too much of the protein to be produced. These findings "might help to establish the etiology of some lung cancers," Dr. Minna said. "They might also help to develop antibody probes to type lung cancer cells, and provide a way to attack the product of the oncogene."

Researchers are also learning about the precursor cells of the various types of human lung cancers. Even though the four major types of human lung cancer appear to have distinct patterns of differentiation, Dr. Minna said, "evidence from some laboratories indicates they may all arise from a common precursor in the epithelial cells of the bronchus." Finding out how these cells differentiate might provide valuable clues for treatment, he noted.

Finally, Dr. Minna said, use of the cell lines has made it possible to prepare single-cell suspensions that can be tested for their sensitivity to drugs and irradiation. So far, such testing has shown that cell lines are responsive to different drug doses; that SCLC cell lines are generally more sensitive to drugs and irradiation than the NSCLC lines; and that SCLC lines derived from patients who have not been treated with drugs are more sensitive than those from patients who have relapsed on chemotherapy. The human lung cancer cell lines may also be used as screening assays to find new drugs, he added.

"These and other studies suggest that the time has come to start prospective tests of human lung cancer cell lines to select therapy for individual patients," Dr. Minna said. He noted that NCI has already started such trials for late-stage SCLC patients and for NSCLC patients. ■

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# MEETING HIGHLIGHTS
continued

## Tooth Enamel Gene Identified by DNA Technology

Pat Sheridan

Using recombinant DNA technology, a team of dental scientists has identified, for the first time, one of the four genes responsible for the production of tooth enamel in humans. This research could eventually lead to the "cloning" of natural fillings for decayed teeth—restorative materials with a structure and durability virtually identical to that of healthy teeth.

National Institute of Dental Research (NIDR) supported researcher, Dr. Malcolm Snead of the University of Southern California School of Dentistry and his associates at Houston's Baylor College of Medicine presented their findings at the IADR meetings.

Progress in genetic engineering has proceeded at a faster pace than was ever anticipated. Four years ago, the production of human insulin and human growth hormone through recombinant DNA technology opened the door to the possibility of using this procedure to tailor-make virtually any protein. These gene-splicing techniques are being applied not only in medicine, but in all fields of industry, and now in the field of restorative dentistry.

Tooth enamel is produced by a careful blend of four different proteins—three amelogenins and one enamelin—each manufactured by its own gene. In studies with mice, the investigators isolated the tissues that produce these proteins and extracted the messenger RNA (mRNA). As its name implies, messenger RNA relays instructions from the DNA—the gene's storehouse of genetic information that tells the gene what to do.

Drs. Snead, Harold Slavkin and colleagues used the newly isolated mRNA to prepare a gene identical to the largest amelogenin. They spliced this mouse gene into strains of common yeast, so that these living cell factories will begin to manufacture the enamel protein as programmed by the artificial genetic machinery. It is hoped that this method will produce carbon copies of the mouse amelogenin protein.

The investigators have also applied these techniques to the studies of human enamel. Using the mouse enamel protein and antibodies to learn more about its human enamel, they found that one of the four enamel proteins in man is very similar in genetic sequence and structure to that of the mouse. This is particularly significant because it demonstrates the usefulness of the mouse gene products in identifying and isolating human tooth enamel proteins.

A number of steps have yet to be accomplished before a new restorative material could become available. The other three proteins must first be isolated and cloned. The research team must then show that the four proteins will combine in the laboratory to form enamel with characteristics identical to the natural tooth.

Despite the extensive work ahead, the investigators see exciting possibilities for the practical application of their research. If the studies continue as planned, dentists in the future will be filling cavities with an enamel-cloned paste that hardens quickly and is identical to the enamel of teeth. Moreover, scientists project that this new substance will look better, last longer and be less sensitive to heat and cold than the currently used silver, gold and plastic restorative materials. These studies are also providing valuable clues to our understanding of both normal and abnormal genetic development in animals and man. ■

## New Method of Application Improves Effectiveness of Antiviral Drug Against Herpes

Pat Sheridan

Scientists at the Medical College of Georgia in Augusta report encouraging news for the millions of Americans who are plagued with recurrent fever blisters caused by herpes simplex virus (HSV). In preliminary patient studies, the antiviral drug Ara-AMP applied by iontophoresis resulted in a pronounced and rapid reduction of herpes virus in orofacial lesions.

This finding emerged following completion of the second stage of a three-phase clinical trial conducted by National Institute of Dental Research-supported scientist Dr. Louis Gangarosa and associates.

None of the numerous antiviral drugs developed has been effective against either oral (type 1) or genital (type 2) herpes. Because the drugs are applied topically, Dr. Gangarosa's research team suspected inadequate penetration, rather than a deficiency in the medications themselves, as the barrier to successful treatment. To test this hypothesis, the investigators turned to a method of drug application called iontophoresis, a process of delivering medications to tissues by an electric current to enhance penetration. Iontophoresis is not a new technique, but its potential for administering a variety of drugs more efficiently has long been overlooked in both medicine and dentistry.

Previous research by Dr. Gangarosa demonstrated dramatic and consistent effectiveness of iontophoresis with vidarabine phosphate (Ara-AMP Ionto) and another antiviral, acyclovir (ACV-Ionto), against oral herpes in guinea pigs—an animal whose lesions closely resemble those of man.

These successful animal studies laid the groundwork for the present three-stage clinical trials. In Phase I, healthy persons received the antiviral by iontophoresis to determine if the procedure would propel the drugs beyond the lesion into the bloodstream. The results pointed up a major benefit of this technique in that antivirals remain localized in the cold sore and do not appear anywhere in the system. In Phase II, 23 patients with recurrent cold sores were divided into three treatment groups: Ara-AMP Ionto, ACV Ionto, and an untreated group. A technician, who did not know which treatment a patient was receiving, cultured a tissue sample from each lesion at the time of the first visit, then once a day thereafter until the virus could no longer be detected.

The results demonstrated that half of the Ara-AMP-treated lesions had no evidence of virus after 24 hours, and 90 percent were virus-free at 48 hours. Herpes virus could still be detected, however, in over 90 percent of the untreated and ACV-treated fever blisters one day after treatment, and in 65 percent at the two-day mark. Nonetheless, acyclovir showed a trend toward more rapid relief of symptoms, a factor prompting the drug's inclusion in the expanded clinical trial. Another valuable finding from this preliminary study points to a reduction in possible treatment side effects because antivirals are delivered locally by iontophoresis instead of systemically.

These positive results have paved the way for the Phase III clinical trial that involves 81 orofacial herpes patients. Patterned after this limited study, the double-blind trial will compare three different treatment approaches: Ara-Amp Ionto, ACV-Ionto, and sodium chloride—an inactive substance that serves as a control. In a double-blind test, neither the patient nor the doctor knows which drug is being given. If the present trends toward reduction of symptoms, virus duration and side effects continue, fever blister sufferers may look forward to a safe effective treatment within the next two years. Moreover, Dr. Gangarosa and colleagues suggest that these initial successes with iontophoretic administration of antiviral drugs may hold promise for the treatment of genital herpes as well. ■

# MEDICAL CAPSULES

Sandra D. Levine

• A recent study has revealed a statistically significant association between alcohol consumption and rectal cancer, and also between alcohol consumption and lung cancer.

The study, funded by the National Cancer Institute (NCI), looked at the relationship between the use of alcoholic beverages and the subsequent occurrence of epithelial cancer at five specific sites (stomach, colon, rectum, lung, and prostate) in 8006 Japanese men in Hawaii.

Information on their alcohol intake (wine, beer, and whiskey) was obtained in the mid-1960s and the subjects were then followed for approximately 14 years (through the end of 1980). The analysis was adjusted to take into account the effects of age and cigarette-smoking.

Data on 7837 of the subjects were analyzed. For three of the cancer sites—stomach, colon, and prostate—there appeared to be no relation to alcohol consumption. For the other two sites—rectum and lung—however, there was a significant trend toward increasing rates with successively higher levels of alcohol use.

It was also evident that whereas rectal cancer was related only to beer consumption, lung cancer appeared to be associated with wine and whiskey use. The suggestion of an association between alcohol intake and rectal cancer was stronger than for lung cancer.

Results of the study were reported in the March 8 issue of *The New England Journal of Medicine*.

• The National Eye Institute (NEI) is sponsoring a nationwide study to determine if a new, investigational drug can prevent or retard the development of diabetic retinopathy and nerve damage in patients with insulin-dependent (Type I) diabetes.

The drug, sorbinil, acts as an inhibitor of aldose reductase, an enzyme that may play an important role in the problems caused throughout the body by diabetes.

The Sorbinil Retinopathy Trial, which will take place at 12 centers across the country, will involve insulin-dependent diabetics 18-56 years old, who have not yet developed diabetes-related eye damage.

Diabetic retinopathy, a common complication of the disease, can cause blindness.

• The National Institute of Allergy and Infectious Diseases (NIAID) has published a new brochure to warn pregnant women about toxoplasmosis, a parasitic disease transmitted by household cats, which can have serious effects on the fetus.

When cats eat birds or mice infected with the parasite *Toxoplasma gondii*, they shed the parasite in their feces. It can then be passed on to humans.

If toxoplasmosis is acquired during pregnancy, the fetus can be infected in anywhere from 15 to 65 percent of women, depending on the stage of pregnancy. Spontaneous abortion, stillbirth, or delivery of a baby with birth defects may result.

Researchers are studying new treatments and the development of more effective diagnostic tests for the disease.

The brochure, which recommends ways to help prevent toxoplasmosis, is available from the NIAID Information Office, (301) 496-5717.

• The number of low birth weight babies born in the U.S. during the decade of the 1970s has declined progressively, according to an analysis conducted in part by the National Institute of Child Health and Human Development (NICHD).

The incidence of low birth weight—2,500g (5 lb 4oz) or less—in preterm infants (less than 37 weeks gestational age) declined 7.1 percent overall. There was a 9.0 percent decline among white infants, and a 5.8 percent decline for black infants.

The incidence of low birth weight in term infants (at least 37 weeks gestational age) declined 20.9 percent overall. Among white infants, the decline was 24.6 percent; among black infants, it was 14.9 percent. This represents a three-fold greater reduction in low birth weight incidence among term infants than among preterm infants.

Birth weight is an important factor in infant survival. Therefore, this trend toward a decline in low birth weight is encouraging. The researchers suggest that several factors may account for this decline. These include reduction of the number of high-risk pregnancies; anti-smoking campaigns; emphasis on good nutrition; and earlier prenatal care.

Results of the analysis were published in the April 20 issue of the *Journal of the American Medical Association*.

• Under a grant from the National Institute of General Medical Sciences (NIGMS), researchers are working on a new drug delivery system—a small implantable pellet.

Dr. Robert Langer and associates at the Massachusetts Institute of Technology are testing a series of copolymers that should make it possible to design a pellet containing a 3-year supply of powdered medication. Trial pellets of ethylene vinyl acetate copolymer with the medication in them are covered with a second copolymer in which small stainless steel spheres are embedded. This device can then be implanted just under the skin where it will release the drug at a steady rate through pores in its surface. The steel spheres will enable the patient to accelerate the rate of drug release by contact with a magnetic source that perhaps could be worn on a belt or watchband.

One of the advantages of the pellet is that the patient can control the drug supply, and the pellet cannot break and release excessive amounts of the medication.

Pellets containing insulin have been implanted successfully in diabetic rats. The researchers believe this delivery system would be appropriate not only for insulin, but also for the administration of other types of drugs which need to be given continuously but slowly, such as medications for inflammatory bowel disease, some heart conditions, and in post-organ transplants. They are also studying the use of biodegradable polymer pellets for short-term drug applications.

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# News&Features from NIH

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**Story On Page 8**

**News&Features**
**from NIH**
August 1984

Oral doses of the experimental drug acyclovir reduce the recurrence rates of genital herpes infections, according to two NIAID studies. Genital herpes is a recurrent contagious viral disease affecting about 20 million Americans.

In one of the studies, treatment with acyclovir prevented recurrences in 68 percent of the 96 patients given the drug and lessened the severity of the episodes that did occur.

Further research on the drug is necessary, however. A large-scale study is currently being conducted to evaluate the long-term safety of acyclovir use. See page 10

The progress that scientists are making in understanding the metastatic process was discussed recently at an NIH Science Writers' Seminar.

Tumor metastasis is a multi-step process by which cancer cells repeatedly penetrate many tissue barriers. When a tumor metastasizes, cancer cells penetrate tissue by attaching themselves to the meshwork that separates one tissue from another. The invading tumor cells then release enzymes that cut holes in the meshwork, allowing the tumor cells to penetrate.

Scientists are working on a new technique using monoclonal antibodies to detect early the spread of tumor cells in the lymph system. See page 6

What kind of exercise and how much can a pregnant woman safely engage in? This question has become more important as the physical fitness movement attracts more women of childbearing age. At a recent workshop sponsored by the NICHD, experts on pregnancy and exercise stated that although conventional wisdom states that pregnant women may safely continue an exercise program started before pregnancy, there is no research to substantiate this notion. They further added that only a few carefully controlled observations have been made in pregnant women and that no data are available concerning the effect of exercise on the first trimester. See page 7.

Twenty years ago, nine out of ten babies born weighing less than three pounds died at childbirth. Today, thanks to progress in research, at least half of these children survive. However, by the time they reach school-age, 60 to 70 percent have handicaps that are severely disabling. Research has shown that many of these conditions have their origins in embryonic development and can be prevented or treated if intervention is begun early. See page 2

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# Early Diagnosis and Treatment—Target of Perinatal Research

Tineke Boddé

"Twenty years ago, nine out of 10 babies born weighing less than three pounds died. Today, more than half live," Mortimer B. Lipsett, M.D., told members of the American Public Health Association recently. Of those who survive, 60 to 70 percent have some handicapping condition by the time they reach school age, such as learning problems, mental retardation, cerebral palsy, blindness and deafness, according to Dr. Lipsett, Director of the National Institute of Child Health and Human Development (NICHD).

In the United States, 250,000 infants are born each year with low birthweight (under 5½ pounds). Some 50,000 of these are very low birthweight infants (weighing less than 3⅓ pounds). In this latter category alone, between 15,000 and 17,500 children will have lifelong physical or mental disabilities.

Congenital malformations, chromosomal abnormalities, and genetic disorders affect another 100,000 infants each year. In these cases, too, those who survive often suffer life-long physical, mental or emotional disabilities.

On the plus side is the growing recognition that many diseases and abnormalities seen at birth have their origins in events during embryonic development, and can be prevented or treated if intervention is known and started early. During the past 15 years, techniques have been developed that help physicians diagnose fetal abnormalities earlier than ever before. At the same time, the number of pregnant women seeking prenatal care has increased.

In view of these advances and the ever growing need for answers, NICHD emphasized in its 5-year research plan released in 1981 that congenital defects and mental retardation were to be considered priority research areas.

Between 1971 and 1974 NICHD sponsored a nation-wide study involving more than 2000 pregnant women to investigate whether amniocentesis adversely affects mother or baby. Researchers found that perinatal problems, fetal loss, low birthweight and birth defects were no more common among women undergoing amniocentesis than among the controls. Amniocentesis involves the analysis of fetal cells found in a sample of amniotic fluid extracted through the mother's abdominal wall during the 16th to 18th week of pregnancy. It allows scientists to detect in unborn babies more than 100 chromosomal abnormalities and inborn errors of metabolism.

To bring together and evaluate all that was known about amniocentesis and other types of antenatal diagnosis, NICHD sponsored a Consensus Development Conference on that topic in 1979. In February 1984, a similar conference was sponsored to assess the risks and benefits of ultrasound, a technique used to view the fetus *in utero* without ionizing radiation. Ultrasound is often used in conjunction with amniocentesis and a more recently developed technique, chorion villus sampling (CVS).

A nurse has just taken a blood sample from the heel of this newborn. The sample will be sent to a state laboratory for routine screening for hypothyroidism.

NIH PHOTO 1960

CVS is an experimental method of prenatal diagnosis that involves withdrawing a sample of tissue from protrusions of a membrane called the chorion, which surrounds the developing fetus. The sampling is done directly through the uterine cervix and allows the detection of many fetal defects as early as the 9th week of pregnancy.

CVS can screen for the same disorders as amniocentesis but it yields results much sooner and at an earlier stage of pregnancy than does amniocentesis. NICHD is presently initiating a research program that will evaluate the safety and efficacy of this new procedure.

Specific conditions which have benefited from recent advances in early diagnosis and treatment procedures include:

*Phenylketonuria:* Because most states in this country require that all newborns receive a blood test for PKU, this enzyme deficiency has virtually been eradicated as a cause of severe mental retardation. About one baby in 11,000 is born with PKU in the United States, but if those affected adhere to a special diet to control the harmful elevation of phenylalanine in the blood, they can grow up normally. With the use of amniocentesis and genetic engineering techniques, NICHD-supported scientists are evaluating and refining a new procedure that can diagnose PKU in unborn children. Studies have been initiated to prevent the harmful effects of high levels of maternal phenylalanine in newborns by dietary treatment of pregnant women who suffer from PKU.

*Hypothyroidism:* In the early 1970s, NICHD-supported scientists developed a sensitive blood test that could identify insufficient thyroid hormone levels in newborns. The resulting condition, hypothyroidism, affects one infant in 4,000 and—unless treated promptly—leads to delayed growth and mental retardation. Most states have since adopted the test as a routine procedure.

*Respiratory distress syndrome (RDS):* Hormones administered to the mother to hasten fetal lung developme and special air pressure treatments to keep the lungs inflated have markedly improved survival of infants with RDS in the last decade. In a more recent development, premature infants with RDS have been given purified lung surfactant extracted from human amniotic fluid. When placed into the neonates' tracheas, the lubricant significantly improved their breathing so that mechanical ventilation could be reduced. Studies are continuing to assess the long-term safety of this experimental treatment.

*Hearing deficiencies:* A group of NICHD-funded psychologists have devised a technique that offers promise for assessing hearing in newborns and other difficult-to-test subjects, including mentally retarded, autistic and hyperkinetic children. The researchers based their technique on the eyeblink reflex which makes testing possible while the subjects are asleep.

*Precocious puberty:* NICHD physicians at the NIH Clinical Center have successfully treated children diagnosed early in life with premature sexual development by giving them daily injections of a synthetic brain hormone analog, luteinizing hormone-releasing hormone (LHRH). In most children, sexual development was reversed by the drug and secondary sexual characteristics disappeared. Treatment was stopped about age 10 or 11 to allow the children to start puberty naturally. Studies continue to assess the drug's long-term effects.

In addition to the above examples, advances have been made in the treatment of hyperbilirubinemia, megaloblastic anemia, cytomegalovirus infection, and other illnesses. Moreover, research is being conducted that some day may lead to the surgical correction *in utero* of such physical disorders as hydronephrosis (a kidney disorder), cleft lip and palate, and neural tube defects, including hydrocephalus. Advances in genetic engineering research hold promise that such disorders as Tay Sachs disease, thalassemia, and sickle cell anemia may be corrected early in pregnancy or prevented altogether in the future by replacing the defective gene on the embryo's or parent's chromosome with a normal one. ■

## Guidelines Issued for the Treatment of High Blood Pressure

Prepared By The National Heart, Lung, and Blood Institute

Dr. Claude Lenfant, Director of the National Heart, Lung, and Blood Institute (NHLBI), has announced the release of the latest report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure. This report reflects current findings on high blood pressure and provides guidelines for physicians in treating patients and for community groups to develop local-based programs. High blood pressure is one of three major risk factors, along with cigarette smoking and elevated blood cholesterol, for the development of heart disease or stroke.

"This report is an update of the previous Committee report published in 1980, and contains new and important information on various levels of disease risk associated with high blood pressure, the nondrug treatment of certain hypertensive patients and the treatment of mild high blood pressure," said Dr. Lenfant. "We believe this will be a useful and informative document for the physicians and other health professionals."

The report defines a diastolic blood pressure of less than 85 mm Hg (millimeters of mercury, the standard reporting unit for blood pressure) as normal blood pressure. A diastolic pressure of 85 to 89 is considered high normal and warrants observation. A repeated reading on two occasions of 90 to 104 is defined as mild high blood pressure, requiring steps to lower it. A 105 to 114 diastolic pressure is moderate high blood pressure, and a reading of 115 or above is severe hypertension. The Committee offers two new categories based on the systolic pressure. Borderline isolated systolic hypertension (systolic pressure of 140–159 mm Hg when the diastolic is less than 90) and isolated systolic hypertension (systolic pressure over 160 mm Hg).

In addition to defining the categories of high blood pressure, the Committee offers guidelines on nondrug treatment, stepped-care therapy (proceeding to the next stage of therapy) and treatment of various special groups such as blacks, children, and pregnant women.

Among the nondrug therapies, the Committee recommends alterations in diet for weight loss for those who are overweight, and suggests that the physician may want to outline a moderate exercise program which may be beneficial even to persons who are not overweight. Among the dietary suggestions, the Committee recommends that patients be advised to cut down on salt (sodium) in the diet. Sodium restriction may also enhance the effectiveness of drugs used to treat hypertension.

"It is encouraging to see that the Joint National Committee continues to place emphasis on nondrug treatment for certain classes of patients," said Dr. Lenfant. "It may be that many patients can avoid drugs altogether if they respond to these forms of treatment. However, even among these mildly hypertensive patients, not everyone will respond to nondrug treatment and the physician should resort to drug treatment for patients who don't respond within a reasonable time."

The 1984 Joint National Committee also formulated guidelines for the treatment of mild hypertension, an area that has been the subject of some controversy. Drug treatment is recommended for individuals with blood pressure in the range of 95 to 104 mm Hg diastolic if the person does not respond to dietary and other nondrug treatment. The Committee considers that the benefits to be obtained by drug therapy outweigh the known risks from such therapy. The Committee recognized, however, that some authorities are reluctant to prescribe drugs for the lowest range of mild hypertension (diastolic 90–94 mm Hg). The physician who elects not to treat mild high blood pressure with drugs is advised to begin rigorous nondrug therapy and follow the patient as closely as if he or she were taking drugs since many of them will deteriorate to the point that drug therapy will become necessary.

Isolated systolic hypertension is found in a significant number of elderly patients, and there is strong evidence that it increases the risk of stroke or illness from other heart-related conditions. There are inadequate data to answer whether reducing the systolic blood pressure also will reduce the person's risk of heart attack or stroke. NHLBI currently is sponsoring a clinical trial to answer this question. For the present, the Committee recommends a trial of nondrug treatment such as sodium restriction or weight reduction where appropriate. If the physician opts for drug treatment, the Committee recommends cautious reduction of systolic blood pressure to the 140–160 range, with further reduction attempted only if the patient has tolerated the initial therapy well. The decision on treatment must be made on an individual basis.

The previous report of the Joint National Committee was published in 1980. The current report is the third one and was issued because recent findings about high blood pressure and its treatment, and new drugs placed on the market to treat high blood pressure, were important factors requiring consideration. ■

# New Drug Therapy Offers Hope for Kidney Stone Patients

Marti Asner

Hope is on the horizon for about 200,000 people in the United States who suffer from calcium-containing kidney stones. Dr. Charles Y. C. Pak of the University of Texas Health Science Center at Dallas has developed a new drug therapy using potassium citrate. Dr. Pak's research has shown that potassium citrate reduces the rate of or stops stone production in patients with low urinary citrate levels. Treatment using this compound has virtually eliminated the need for surgery in patients suffering from calcium-containing kidney stones. The use of potassium citrate in treating calcium-containing kidney stones is awaiting approval by the Food and Drug Administration (FDA).

Low urinary citrate, or hypocitraturia, affects about 50 percent of all people requiring medical treatment for kidney stone disease. It can be caused by chronic diarrhea, high animal protein intake, or renal tubular acidosis. Hypocitraturia may coexist in some people along with hypercalciuria (high urinary calcium). In these patients, potassium citrate can be used in combination with other drug treatments.

Dr. Pak tested the drug in 78 patients suffering from hypocitraturia. The results showed that 74 percent stopped forming stones while taking the drug; 96 percent had a reduced rate of new stone formation. The rate of stone formation increased when patients stopped taking the drug.

Potassium citrate is a component of orange juice. But Dr. Pak says, "to provide enough potassium citrate a person would have to drink one quart a day, which many people could not tolerate. Also, orange juice contains calcium and sugar. Both components may raise urinary calcium. Then there is the high cost and sometimes unwanted calories."

A kidney stone is a hard mass that builds up gradually when various salt or mineral crystals deposit on the inner surfaces of the kidney. Sometimes a stone will break away and move down the urinary tract, causing severe pain and bleeding. In the United States, there are about 500,000 new cases each year.

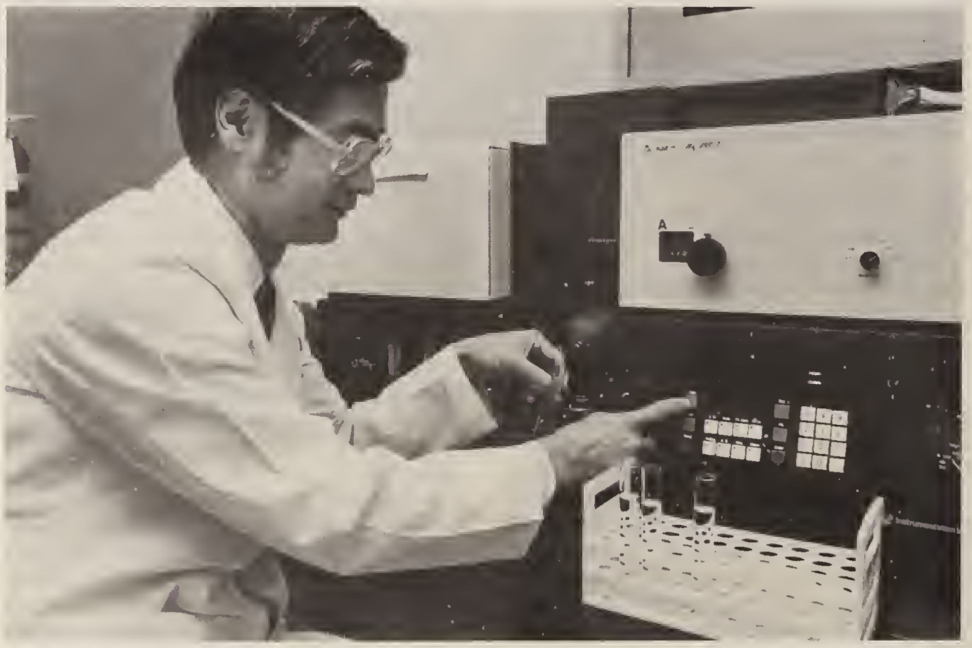
Dr. Pak and his colleagues have been studying the medical management of renal stones for about 15 years. The cause of kidney stone disease can now be determined in nearly 95 percent of patients, and new stone formation may be prevented in the majority of patients using a variety of selective medical treatments. There are at least eight different causes of kidney stone disease, and Dr. Pak has described specific treatments for each of them.

In 1982, the FDA approved another of Dr. Pak's drug treatments for kidney stones—sodium cellulose phosphate which is being used to treat absorptive hypercalciuria, a disease associated with increased absorption of calcium from food.

"The primary objective of medical treatment," said Dr. Pak, "is the prevention of new stone formation. With the combined application of improved techniques for removal of stones and the progress in medical therapy, the control of renal stone disease may well be in hand."

Dr. Pak conducted his research at the General Clinical Research Center (GCRC) under a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. General Clinical Research Centers are special study units where clinical investigators and patient volunteers work together to decipher complex disease processes. In this tightly controlled environment, researchers are able to perform precise tests and regulate patient diets down to the gram. There are 74 GCRCs in the United States funded by the Division of Research Resources (DRR).

"My work on kidney stones could not have been completed without the controlled environment of the General Clinical Research Center," said Dr. Pak. "The inpatient facility, with provisions for constant diets and trained staff, was essential for elucidation of physiological action and pharmacology of this drug, while the outpatient facility was critical for sessing long-term response treatment." ■



Kidney stone expert Dr. Charles Y. C. Pak, Professor of Internal Medicine at the University of Texas Health Science Center at Dallas and Director of the General Clinical Research Center cently announced the development of a new drug therapy for kidney stones using potassium rate. Dr. Pak's research shows that potassium citrate, a component of citrus juices, reduces the rate of or stops stone production in patients with low urinary citrate levels.

NIH PHOTO 1961

# Magnetic Resonance Imager Provides Detailed Pictures of Body's Organs Without Invasion

key Hanlon

Scientists and physicians at the National Institutes of Health are using the latest medical diagnostic scanner to diagnose brain disorders and cancer. The Magnetic Resonance Imager (MRI), commonly known as the Nuclear Magnetic Resonance (NMR), scanner makes pictures of the body's interior without harmful radiation and without the use of catheters or contrast agents.

This new technology uses a strong magnetic field and radio waves to provide detailed images of the body's organs. It is being used at the Clinical Center's Diagnostic Radiology Department, to diagnose strokes in the elderly, abnormal growth patterns in children, multiple sclerosis, and disorders of the central nervous system. It can diagnose brain disorders ranging from seizures to brain tumors and cancer ranging from Hodgkin's disease to cancer of the esophagus.

It works by enclosing the body in a powerful magnetic field and then measuring, by means of radio waves, the effect the field has on the atomic nuclei within the body. The patient is placed into the diagnostic machine, which contains a static magnetic field that is approximately 10,000 times greater than the earth's magnetic field. The magnet first aligns some of the body's atomic nuclei then disrupts the alignment with an energizing radio signal that temporarily excites the nuclei. After the signal ends, the nuclei surrender their excess energy as they return to their alignment position. The computer converts these excess energy signals into an image.

The new device is more versatile than the CT scanner (computer tomography). MRI can differentiate blood vessels, nerves, and soft tissue in any organ without using ionizing radiation and without piercing the patient's skin. Because the images are not blocked by bone, it can produce a clear view of the body's underlying tissues, making it more effective than CT in looking at the brain, brain stem, and spine.

Since 1981, thousands of patients have been safely scanned by MRI. All indications are that the procedure is harmless because the radio waves are of very low energy. The only hazard appears to be that the magnet can pull loose objects such as keys, pens, and stethoscopes into the machine. It has also been known to stop watches and erase information on magnetic strips of credit cards. All metal objects are removed from persons entering the magnetic field to avoid any harm to the patient.

Image shows sagital (front to back) view of brain as patient is prepared for MRI scan.

NIH PHOTO 1962

Because of its strong magnetic field, MRI may also be harmful to patients with electronic pacemakers, permanent surgical clips on blood vessels, or prosthetic devices. Scans are not routinely performed on such patients.

While clearly a major breakthrough in diagnostic radiology, MRI has some disadvantages. It takes longer to produce an image than CT, requiring several minutes per picture. The CT requires only two seconds to make a similar image. MRI examinations can take between 45 minutes and two hours to complete. The diagnostic machinery is currently more expensive than CT, costing in the $2 million range as compared with a $1 million price for CT.

It is the beginning of a new era of high technology in medicine. Still in its infancy, MRI is a valuable diagnostic tool, providing outstanding advantages in medical research. ■

# NIH Science Writers' Seminar Focuses on Cancer Metastases

Bobbi Bennett

Despite remarkable advances in cancer treatment, most cancer patients die of metastases. The progress that intramural scientists are making in understanding tumor invasion and metastasis, and the possible application of their findings in detecting, preventing, or eliminating metastases was the focus of a recent NIH Science Writers' Seminar.

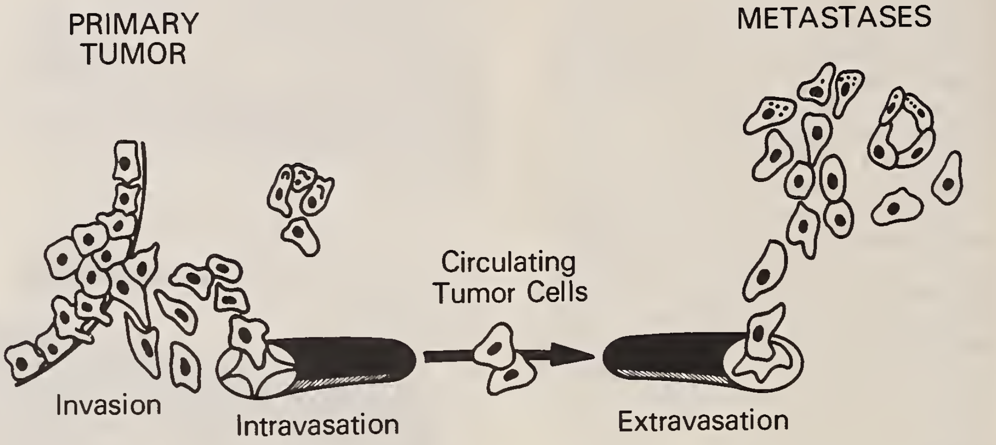
The moderator, Dr. Lance Liotta, Chief, Laboratory of Pathology, National Cancer Institute (NCI), described the multi-step metastatic process by which tumor cells repeatedly penetrate many tissue barriers. One of these barriers is the extracellular matrix, a dense meshwork that mechanically supports tissue and separates one tissue from another.

The first step in the metastatic process is attachment of the tumor cell to the basement membrane, one component of the extracellular matrix. This attachment may be facilitated by laminin, a protein found only in the basement membrane. Dr. Liotta and his associate, Dr. Terranova in the National Institute of Dental Research (NIDR), have found that there is an increased number of exposed laminin receptors on the surface of an invading tumor cell. An assay which they developed to measure these receptors should yield information potentially valuable in predicting the aggressiveness of a patient's tumor.

Dr. Liotta's group also has found that a fragment of the laminin molecule can bind to the receptor and block the attachment of tumor cells. This fragment can inhibit or abolish metastatic formation in the lungs of mice with melanoma.

The second step in invasion by a tumor cell is its release of enzymes that cut holes in the matrix allowing the cell to move through this barrier. Dr. Liotta and his colleagues have isolated and purified an enzyme—augmented in certain types of tumor cells—that selectively degrades type IV collagen, the protein which forms the backbone of the basement membrane. They have used an antibody directed against this enzyme to identify microscopic metastases in the lymph nodes of patients with breast cancer. This test could potentially be used to determine the presence or likelihood of metastases.

Dr. Liotta pointed out that several laboratories are studying other binding factors and enzymes that may also play a role in the tumor cell's attachment to and destruction of the extracellular matrix.



The complex process of metastasis begins when tumor cells in the primary tumor acquire the ability to invade the surrounding host tissue. Next, they invade the walls of the blood vessels or lymphatics (intravasation) and enter the circulation until they are arrested in the target organ. The arrested tumor cells must invade through the walls of the blood vessel (extravasation) and then initiate the new tumor growth in the target organ or tissue. NIH PHOTO 1963

Dr. James Talmadge, Head, Preclinical Screening Laboratory, Program Resources, Inc., NCI Frederick Cancer Research Facility, discussed different properties of cells (sensitivity to a drug, the ability to metastasize) found in primary tumors and metastases. These different properties or heterogeneity of cells within individual metastases as well as among metastases may be the most formidable obstacle to the successful treatment of metastases.

To circumvent this heterogeneity, Dr. Talmadge's group is using activated macrophages—cells which ingest foreign particles such as bacteria. *In vitro* studies have shown that these macrophages can mediate the destruction of tumor cells independent of such tumor characteristics as antigenicity and drug sensitivity. Furthermore, efforts so far to select tumor cells resistant to tumoricidal macrophages have been unsuccessful.

Dr. Talmadge and his group have shown in animal studies that activation of macrophages by biological response modifiers can increase the survival of animals with spontaneous metastases to the point where one could consider them cured.

Unfortunately, activated macrophages are unable to control more than $5 \times 10^7$ tumor cells. Since the current limit of our diagnostic capabilities is $10^9$ cells, this means that most tumors would not be agnosed early enough to use this approach. However, Dr. Talmadge has shown in animal studies that if the tumor is first decreased by chemotherapy and radiotherapy, then the activated macrophages can handle the residual disease. He pointed out that this multimodal approach works only if the cytotoxic agent can be used in doses which do not impair the immune response.

Dr. John Weinstein of NCI's Laboratory of Mathematical Biology described his efforts to use a more direct and effective route for delivering monoclonal antibodies to a major site of metastasis, the lymph nodes, than the commonly used method of intravenous injection.

Tumor cells which escape the primary tumor can pass not only into the bloodstream but also into the lymphatics which drain fluid, large molecules, and cells from tissues all over the body. Via this route, tumor cells can enter lymph nodes located in the armpits, groin, neck, and elsewhere and form metastases. These metastases are often the first evidence that a tumor is spreading.

In animal experiments, Dr. Weinstein found that radiolabelled monoclonal antibodies injected subcutaneously follow the same lymphatic route as the tumor cells and bound with high efficiency to the metastases in the lymph nodes.

Using gamma camera imaging, he was thus able to detect very early metastases.

This technique represents a significant advance because it can detect approximately one three-hundredth of the amount of tumor detectable by today's X-ray, CT scanning, or nuclear magnetic resonance imaging, and a much smaller amount than that detected by intravenous administration of radiolabelled antibodies.

Use of this technique would be limited to the detection of lymph node metastases which are at an early stage, i.e., ones that have not yet grown large enough to obstruct the lymph flow. Dr. Weinstein also pointed out that a "cocktail" of several monoclonal antibodies will probably be required to detect all metastases due to their heterogeneity.

Advantages to this route include the use of smaller doses of monoclonal antibodies with a corresponding reduction in toxicity and the avoidance of cross-reactivity with normal cells which can be a problem when the intravenous route is used. (In most cases, cross-reacting normal cells are not present in the lymph system.)

Clinical studies of the lymphatic approach to detecting metastases have just begun. Dr. Weinstein's long-term goal is to see if this technique could be used to kill cancer cells selectively, either by marking them for destruction by the body's own defense mechanisms or by attaching a drug, toxin, or radioactive atom to the antibodies. ■

# Workshop Held on Physical Activity in Pregnancy

Maureen Gardner

What kinds of exercise are safe during pregnancy? What levels of various exercises are advisable? How does exercise affect a pregnant woman and her unborn child?

As the physical fitness movement attracts more and more women of childbearing age, these questions become increasingly important. Precise answers are seldom available, however, because few studies have been performed on exercise during pregnancy.

The National Institute of Child Health and Human Development (NICHD) is working to remedy this shortage of knowledge. In a workshop sponsored by NICHD, experts on pregnancy and exercise surveyed current research and outlined steps to resolve some of the questions about this area. Next, the Institute plans to encourage research that will lead to a better understanding of pregnancy and physical activity.

"Pregnant women today generally are told that they should not take up a strenuous exercise regimen, but that they may safely continue a program started before pregnancy," according to the workshop's coordinator, Dr. Donald McNellis, medical officer in NICHD's Pregnancy and Perinatology Section. While this may seem a common-sense approach, "at this time there is little research to back it up," said Dr. McNellis.

Studies of pregnancy and exercise in both humans and animals were examined in the workshop. The participants represented varied specialties: obstetrics and gynecology, exercise physiology, pediatrics, nutrition, ultrasonography, pathology, behavioral psychology, epidemiology, and bioethics.

"Only a few carefully controlled observations have been made in pregnant women," according to the workshop report, published in the April 1984 issue of the *American Journal of Perinatology*. It states that "no data are available concerning the effect of exercise upon first trimester events."

As for later in pregnancy, one preliminary study of moderate bicycle exercise begun at the 20th week of pregnancy showed "no impact on the outcome of pregnancy," in terms of the length of pregnancy, the events surrounding delivery, or the birthweight of the infant. Nevertheless, the need for further research is clear, as shown by findings in animals.

The report states that despite the limitations of using animals as models for exercise during pregnancy, "several important conclusions have been reached" from animal studies. For example, in pregnant sheep, strenuous exercise such as running, decreases blood flow to the uterus, causing oxygen levels in the fetus to fall. In addition, exercise raises body temperature in both the mother and the fetus, but in animals the temperature of the fetus remains high after the mother's temperature becomes normal.

The effects of these and other changes in the fetal environment during maternal exercise should be investigated in future animal studies, and in humans "when safe and feasible techniques become available," the report recommended.

For research in women, the report urged investigators to be specific when defining the nature of the exercise studied, to note the temperature in the exercise room, and to study changes in a pregnant woman's heart rate during exercise. Researchers were also advised to collect information on weight gain during pregnancy, dietary intake, complications of pregnancy, and infant health, including birth weight, growth and behavior.

Women who are not pregnant respond to exercise through hormonal, nutritional, metabolic and cardiovascular changes. Not enough is known about these ways in which pregnancy alters these responses. The workshop participants therefore concluded that future research should examine not only the effects of physical activity on pregnancy, but also the effects of pregnancy on physical activity. ■

# Scientists Identify a Virus that May Be Linked with Rheumatoid Arthritis

Bill Hall

Scientists have identified a virus in the joint linings of people with rheumatoid arthritis that may be the cause of the disease.

Rheumatoid arthritis is a chronic disorder characterized by inflammation and thickening of the synovial tissues that surround and lubricate the joints of the body. Affecting more than seven million Americans, the disease can lead to bone deterioration, deformity, and eventually, disability. It can be very mild in some people, while others may suffer severe crippling effects. Immune abnormalities, genetic factors, and infectious agents, including viruses, have all been studied as possible causes of rheumatoid arthritis, but, to date, no cause or cure has been established.

In previous investigations, scientists have observed immunological disturbances associated with chronic joint inflammation in rheumatoid arthritis patients. Researchers believe that these disturbances might be triggered by an agent such as a virus. Now, Dr. Carol A. Smith of the Montefiore Medical Center in New York, collaborating with Drs. Robert W. Simpson, Laurel McGinty, and Lee Simon at Rutgers University, and Drs. Carol W. Godzeski and Robert Boyd of the Eli Lilly pharmaceutical company, believe they have located the viral particle that could be related to the immunological disturbances observed in rheumatoid arthritis patients.

The virus, designated RA-1, shows similarities to parvoviruses which have been linked to certain diseases in dogs, cats, and mice. Only recently have they been associated with human disease, specifically in a chronic form of anemia found among black children in Jamaica.

Rheumatoid arthritis affects over seven million Americans and can cause severe crippling effects involving bone deterioration, deformity, and disability (Photo courtesy of the Arthritis Foundation.) NIH PHOTO 1964

The researchers have not been able to grow the RA-1 virus in culture, but they have maintained it for further studies by injecting samples of the virus taken from rheumatoid arthritis patients into the brains of newborn mice. The mice experienced symptoms similar to those that may occur in arthritis, such as loss of hair, tremors, convulsions, and crippling of limbs. Extracts from the mouse brain infected with the RA-1 virus were then injected into rabbits to obtain antibodies to the virus. Using these antibodies to test the presence of viral antigen, scientists found that 13 to 14 samples of joint tissue from patients with rheumatoid arthritis showed evidence of the virus.

The researchers also used the antibodies to test specimens taken from eight patients with osteoarthritis, a separate form of arthritis usually associated with the degeneration of joint cartilage. None of these eight specimens demonstrated the presence of the viral antigen, thus increasing the possibility that the RA-1 virus could be related to rheumatoid arthritis.

However, their findings need to be confirmed through further laboratory research and testing. It may be possible that the RA-1 virus is a cause of rheumatoid arthritis, or it may simply reside in the diseased joint tissue. The authors are cautious and state that the link with human rheumatoid arthritis is "yet undefined." According to Dr. Smith, "The real thrust of future studies will be to try to relate the virus to the immunological activities that are occurring in RA patients, and then make comparisons to similar tests done on people with other forms of arthritis and other chronic diseases. Then we can begin to determine if the RA-1 virus is actually causing rheumatoid arthritis."

The research was supported in part by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), and the National Institute of Allergy and Infectious Diseases (NIAID). ■

# Research Efforts Improve Wound Repair

Doris Brody

How can wound healing be improved— especially for the elderly and people with underlying diseases that cause them to heal more slowly? What cellular and molecular factors promote or impede wound repair? How can skin be made to grow over large wounds and the development of scar tissue be prevented? Grantees of the National Institute of General Medical Sciences (NIGMS) Trauma and Burn Program are seeking answers to these and other questions about various aspects of wound healing.

Traumatic injuries set in motion a series of complex processes by which the body repairs itself. The blood clots, the immune system musters defense against invading bacteria, and scavenger cells digest damaged tissue as well as foreign particles. Eventually the blood vessels repair themselves and new cells migrate into the wound area, where they take hold and begin to grow. Each one of these natural processes involves complicated reactions at the cellular and molecular levels.

In an effort to speed up and improve wound healing, many researchers studying the basic processes involv Dr. Thomas Hunt of the University of California, San Francisco, heads an NIGMS-supported research center devoted to the study of various aspects of wound repair.

There are a number of agents that can either promote or inhibit the rate of wound healing. These include growth factors (which can specifically stimulate the increased production of such components as platelets, which are essential for blood clotting; epidermal or outer skin cells; and connective tissue), hormones, nutritional elements, and oxygen. One goal of the center is to purify growth factors and study their effects on healing.

Dr. Hunt and his colleagues have recently isolated a substance called angiogenesis factor from the fluid in rabbit wounds. The angiogenesis factor is a powerful stimulant of the growth of blood vessels and thus has an important role to play in wound repair.

Although this factor has not yet been isolated from human wounds, the researchers believe it is there because extracts of human wound fluid stimulate blood vessels to grow in rabbit tissue. If human angiogenesis factor could be purified or synthesized, it might be valuable in treatment, especially for wour that are difficult to heal.

Angiogenesis factor also acts in tumors to increase the growth of the blood vessels that supply their nourishment. Thus, in addition to trying to isolate and purify the human angiogenesis factor, scientists in Dr. Hunt's laboratory are seeking an antibody that would destroy or neutralize the factor. This might someday contribute to cancer treatment.

Dr. Hunt is also studying the relationship of oxygen to the healing process. It is well known that wounds heal better and resist infection more effectively if their blood and oxygen supplies are good. However, in the past there has been no satisfactory way of measuring oxygen supply to tissues. Dr. Hunt and his colleagues have now patented a simple device for measuring oxygen tension in human tissue. The device, which resembles an intravenous needle, has been used in several hundred patients and has proved extremely valuable in deciding when blood transfusions or fluids are necessary. Recent studies by these researchers using the device have shown that exposing guinea pigs to high levels of oxygen, especially during the first four hours after infection, greatly increased the animals' ability to retard bacterial growth.

The body's efforts to heal itself can cause scarring and distortions of muscle tissue called contractures, which may result in major disfigurement and seriously impaired movement. In order to learn how to minimize these consequences of severe injuries, NIGMS grantees are studying the cellular and molecular events behind them.

Dr. Paul H. Ehrlich at Massachusetts General Hospital in Boston is examining the role of the connective tissue matrix in the formation of scar tissue. This matrix is an intricate structure composed of proteins and other molecules which holds cells together in tissues and holds tissues together in organs.

Dr. Ehrlich is studying freeze injuries as well as burn injuries, because although both kill cells, those caused by freezing do not leave contractures when they heal. This may be because after freeze—but not burn—injury the connective tissue matrix is still in place. Dr. Ehrlich believes that even though its cells are dead, this matrix serves an important function in guiding orderly cell regrowth. Understanding the specific factors involved may help scientists design ways to control cell growth after other types of injury.

A mutant "tight skin" mouse model being developed by Dr. Ehrlich and his colleagues may help answer related questions about wound repair. These mice heal more slowly than normal mice do and develop serious scars which, for some reason, do not lead to contractures. The scientists are studying the possible reasons for this phenomenon with the hope of learning ways to prevent excessive scar tissue formation in humans. ■

# As the Virus Moves: Neurology Laboratory Tapes Molecular Journey

Lynn J. Cave

The work has all the trappings of a major television production, straight from the special lighting down to the three months of rehearsal to get everything right.

Captured on video tape is a science docudrama about intracellular transport, a mechanism essential to a cell's normal functioning. What unfolds before the viewer is something that has never been seen before—the actual movement of viral molecules on their journey from the center to the periphery of the living cell.

In this production, the molecules are unassembled pieces that will make up part of the virus's outer covering, or envelope. But some day similarly produced video tapes may be used to examine how cells transport other molecules, such as neurotransmitters, which play a role in diseases like Parkinson's.

Directing this unusual experiment is Dr. Heinz Arnheiter, a Fogarty International Center (FIC) Visiting Associate who has worked in the NINCDS Laboratory of Molecular Genetics for the last three years. Collaborating with him on this work are Dr. Monique Dubois-Dalcq, also of the Laboratory of Molecular Genetics, and Dr. Bechara Kachar of the NINCDS Laboratory of Neurobiology.

By manipulating cells with a technique called microinjection and watching the activity with a low-light-intensity video camera, Dr. Arnheiter has made cells into living test tubes.

"As soon as you can do something in a test tube, you can control the experimental conditions very carefully," says Dr. Arnheiter. Gaining control of experimental conditions is very important to scientists who must break complex events down into simpler ones to study them, he says.

Dr. Arnheiter's living test tubes are laboratory-grown cells in which a virus related to the rabies virus is living and making copies of itself. To perform the microinjection technique, Dr. Arnheiter uses the visual control of a microscope to position a fine-tipped glass pipette over a slide containing the virus-infected cells. The cells are illuminated by a light source that has been carefully adjusted so that the cells don't dry up and die.

Dr. Arnheiter selects a cell and pierces it with the pipette, injecting antibodies that attach only to the virus component he is interested in. The antibodies are tagged with a fluorescent dye, which allows the viral molecules to be seen as bright white spots on a television screen. Because of the exacting nature of the technique, it will take Dr. Arnheiter, a cell biologist, half an hour to microinject 100 cells—this is about 10,000 times fewer than the number of cells most biochemists use in their experiments.

Since perfecting the technique earlier this year, he has taped a total of 7 hours of viral molecules moving from the inside of cells, where they are synthesized, to the outer membrane, where, along with other components, they are assembled into viruses. Although the actual assembly cannot be seen, the tapes show a definite accumulation of viral components at the membrane, Dr. Arnheiter says.

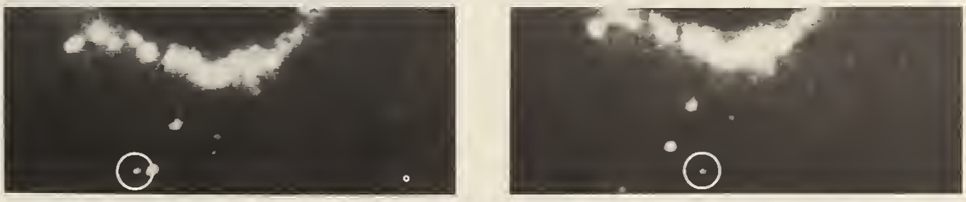
Cells are constantly moving molecules around, he says. And that movement is not random. "Cells have a way of determining up and down and left and right in order to direct the transport of components to specific locations," he says. "Often there is a long distance between where important molecules are made and where they are finally deposited."

An extreme case of such long-distance transport occurs in the neuron. Neurotransmitters made in the cell body must be transported to the tip of the axon, a length that could be up to one meter in some human nerve cells.

Transport of molecules occurs in more than one direction, but like a divided highway, one pathway may be used for conveying substances in one direction and another used for movement in the opposite direction.

"We are interested in determining how the cell directs all this movement without mixing up the traffic lines," the NINCDS-supported scientist says. "We are also interested in how the cell decides where to put certain molecules."

By watching the transport as it occurs, Dr. Arnheiter hopes to find the answers to these basic questions. He will continue this work in his native country, Switzerland, at the University of Zurich, to which he has recently returned. ■



In these photographs, taken two seconds apart from a video monitor, the circled spots show the movement of an antibody—tagged viral molecule as it travels toward the periphery of a cell.

NIH PHOTO 1965

# Acyclovir Reduces the Frequency of Recurrent Genital Herpes Infections

Pat Randall

Daily doses of oral acyclovir, an experimental drug not yet available for general use, effectively reduced the rate of recurrent genital herpes infections in otherwise healthy men and women, according to two studies supported by the National Institute of Allergy and Infectious Diseases (NIAID).

Both groups of investigators stress that while these studies are very promising, further investigations are necessary to evaluate the potential for problems with drug resistance and long-term safety. A large-scale, multicenter study is underway to provide more information about long-term use.

Genital herpes is a recurrent contagious disease caused by herpes simplex virus and usually spread by sexual intercourse. It affects an estimated 20 million Americans. At least 300,000 new cases occur annually, particularly among sexually active young adults and adolescents.

Symptoms generally appear 4 to 10 days after exposure to the viruses and include small, painful blisters on the vagina, cervix, urethra, and anal area in women, and on the penis or around the anus in men. Local swelling and flu-like symptoms may also occur. In a first infection, symptoms generally disappear within 3 weeks.

After the initial infection, the viruses migrate up the sensory nerves near the sore. When they reach the nerve cell center or ganglion, the viruses become inactive, or latent. In most people, the viruses will later be reactivated and cause new sores near the site of the first outbreak. No one knows exactly what brings on a recurrence, although they are sometimes associated with other infections, menstruation, emotional upsets, and sexual intercourse.

There is no cure for genital herpes, but two forms of acyclovir have been approved for treating herpes patients under certain circumstances. An ointment and an intravenous solution are available under the name Zovirax from Burroughs Wellcome Co., Research Triangle Park, N.C. Acyclovir ointment speeds healing of sores and reduces viral growth during the first episode of genital herpes. The intravenous form may be used in patients with severe first episodes of genital herpes and to treat immunocompromised patients with severe oral and genital herpes infections. Neither approved form of the drug affects the rate of recurrences. Acyclovir in capsule form has been used experimentally to relieve symptoms and shorten episodes of initial and recurrent episodes of genital herpes.

All participants in the double-blind, placebo-controlled studies had histories of unusually frequent recurrences of genital herpes, averaging 12 to 16 episodes a year. Most individuals with recurrent herpes experience three to four episodes each year.

Patients received either placebo or acyclovir (400 mg., 600 mg., or 1000 mg. each day) in 200 mg. capsules for up to 125 days with few side effects. The frequency of recurrent infections was markedly reduced in patients taking acyclovir. The amount of the daily dose did not significantly affect the results. After the treatment period was completed, the number of herpetic episodes returned to pretreatment levels in all patients.

One study was headed by Stephen E. Straus, M.D., Head of the Medical Virology Section of NIAID's Laboratory of Clinical Investigation. A treatment course consisted of a placebo or acyclovir capsule given three times a day for 125 days or until herpes recurred. In all, 35 courses of oral acyclovir were given to 31 patients; only six courses were interrupted by herpes recurrences.

Testing of herpes viruses isolated during outbreaks in acyclovir-treated patients revealed some drug-resistant virus. Although post-treatment recurrences in the same patients were associated with drug-sensitive virus, Dr. Straus and his colleagues expressed concern that long-term treatment with acyclovir might favor increased drug resistance.

The second study was done at University of Washington Herpes Research Clinic, Seattle, Wash., and headed by Lawrence Corey, M.D., University of Washington and the Children's Orthopedic Hospital. It was supported by gran from NIAID and the Burroughs Wellcom Co. In this study, 143 men and women completed 120 days of treatment with either placebo, two capsules of acyclovir each day, or five capsules of acyclovir each day. The patients were followed for an additional 120 days without treatment.

Before treatment, the patients had reported a mean of 1.04 recurrences of genital herpes each month. Treatment with acyclovir completely prevented recurrences in 68 percent of the 96 drug-treated patients, reduced the frequency of overall recurrences to 0.14 recurrences per month, and reduced the severity of episodes that did occur.

The investigation at NIAID was done by Dr. Straus, Howard E. Takiff, M.D., Mindell Seidlin, M.D., Lloyd Lininger, Ph.D., Karl A. Western, M.D., Holly A. Smith, and David W. Alling, M.D., Susan Bachrach, R.N., Clinical Center, John J. DiGiovanna, M.D., National Cancer Institute; Sandra Nusinoff Lehrman, M.D., and Teresa Creagh-Kirk, M.S., Burroughs Wellcome Co.

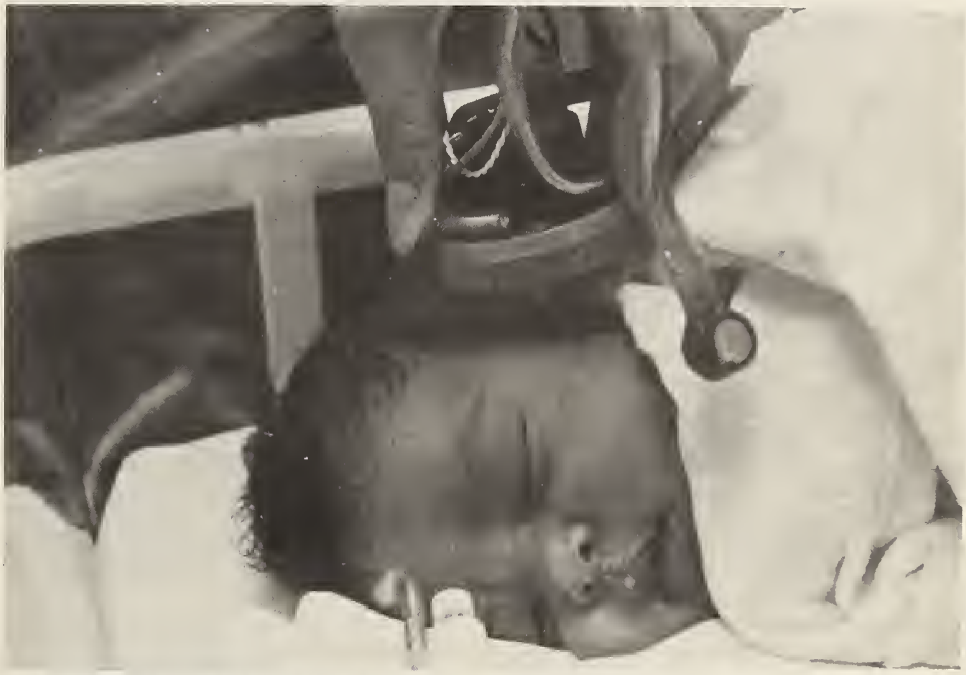
The investigation at the University of Washington was done by Lawrence Corey, M.D., John M. Douglas, M.D., Cathy Critchlow, M.S., Jacqueline Benedetti, Ph.D., Gregory J. Mertz, M.D., Anita Fahnlander, R.N., Michae Remington, P.A., and Carol Winter, R.N., from the Departments of Laboratory Medicine and Medicine, U. of Washington; and James D. Connor, M.D., and Marie A. Hintz, Ph.D., Department of Pediatrics, U. of California at San Diego.

The studies were reported in the June 14 issue, *The New England Journal of Medicine*. ■

This is an electronmicrograph (EM) negative stained picture of a complete herpes virus magnified at 275,000. (Photo courtesy of Dr. J. Almeida and Burroughs Wellcome Company)
NIH PHOTO 1966

# NICHD Researchers Refine Technique to Test Hearing in Sleeping Newborns

Tineke Boddé



An earphone with attached eyeblink monitoring device is being put into place to test the hearing of this 26-hour old sleeping infant. A tap unit in front of the child's glabella evokes the measured eyeblink response. Eyeblink increases when tone is presented with a tap. (Photo courtesy of Department of Psychology, Bryn Mawr College, PA.) NIH PHOTO 1967

Using the body's eyeblink reflex, researchers have refined a technique that may lead to an accurate hearing test for 1-day-old infants. Working with National Institute of Child Health and Human Development (NICHD) support, psychologists Howard Hoffman, Ph.D., and his colleagues Michelle E. Cohen, Ph.D. and Linda E. English of Bryn Mawr College in Pennsylvania, based their tests on the glabella reflex, an eyelid closure evoked by a tap on the area between an infant's eyebrows.

The technique circumvents two major problems usually encountered when testing babies: the changeability of their state (alertness, drowsiness and sleep), and the difficulty of learning a response that can be used to assess hearing acuity tests.

The researchers found that the size of an infant's eyeblink increased when a tone is presented simultaneously with a glabella tap. This unlearned change in the size of the response indicated that the baby being tested "heard" the tone. Dr. Hoffman and his associates found that the eyeblink reflexes of sleeping babies increased when tones of 70, 80 and 90 decibels were used with the reflex modification procedure. Newborns were more sensitive to the tone stimulus than adults.

"Our research is designed to find out how early this change in eyeblink shows up in babies," Dr. Hoffman said. "Our long range goal is to be able to use this phenomenon to detect hearing losses in newborns," he added.

"It is well known that hearing impairment in children often goes undetected. In such cases the child may be thought to be uncooperative or even disturbed or retarded when, in fact, the problem is one of sensory loss. The availability of an easily administered, objective test for hearing could be of considerable value in such cases," Dr. Hoffman said.

An estimated 70,000 children under age five suffer some degree of hearing loss. "Measures to correct their deficiencies are most effective if the impairment is diagnosed and treated early," said Dr. Norman A. Krasnegor, Chief of NICHD's Human Learning and Behavior Branch, which administers Dr. Hoffman's grant.

The infants tested in the experiments ranged in age from 13 to 90 hours. The eyeblinks were measured by a miniature photo-reflective densitometer placed in front of the baby's eye and attached to an earphone through which the tones were presented. The equipment was acceptable to parents, neonatologists, pediatricians and nurses who observed the test sessions, according to Dr. Hoffman.

The children themselves usually slept through the entire test "which shows the utility of this type of methodology," Dr. Krasnegor said.

The reflex modification technique will also be very useful in testing older children who have been identified as mentally retarded, brain damaged or emotionally disturbed. It will help specialists determine whether the youngsters' frequent failures to show normal language development is related to loss of hearing, Dr. Krasnegor said.

A report on the findings of Dr. Hoffman's research team was presented at a recent meeting of the Eastern Psychological Association in Baltimore, MD. ■

# Scientists Honored for Achievements in Cancer Research

Sandra D. Levine

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Twenty-three years ago, biophysicist Dr. Barnett Rosenberg conducted a physics experiment intended to study the effects of electromagnetism on cells. That experiment, through the accidental results it yielded, has saved many lives and earned Dr. Rosenberg the 1984 Charles F. Kettering Award for his outstanding contribution to the treatment of cancer.

Dr. Rosenberg is one of the four 1984 winners of the General Motors Cancer Research Foundation Awards. The prizewinning research of all the 1984 awardees was supported by the National Cancer Institute (NCI). At the time he made his discovery, Dr. Rosenberg's work was being funded by the National Institute of General Medical Sciences (NIGMS). Considered the Nobel prizes of cancer research, the awards are given annually to recognize recent advances and to stimulate further achievement.

The Foundation gives three awards, each consisting of $100 thousand, a gold medal, and $30 thousand to support a conference or workshop led by the winner. Selections are made by an Awards Assembly of 30 prominent scientists from all over the world, chaired by Dr. Jonathan Rhoads of the University of Pennsylvania.

NIH, where the awards recipients delivered lectures about their work on June 13, is the only institution in the world to boast more than one prizewinner. Of the 22 winners since the awards were first given in 1979, four have been NIH intramural scientists.

Dr. Rosenberg's serendipitous experiment involved placing platinum electrodes in a dish of bacteria to see if electromagnetic radiation affected cell growth. During the course of the experiment, platinum ions (the electrode metal) leached into the medium, with the result that the bacteria turned into long filaments and stopped dividing. Dr. Rosenberg speculated that perhaps platinum could do the same thing with wildly dividing cancer cells.

Prior to this, physicians had considered heavy metals such as platinum too toxic for use, but Dr. Rosenberg began testing several platinum compounds in animal tumors.

One compound, cis-diamminedchloroplatinum (II), a combination of platinum and chloride, demonstrated remarkable anti-tumor activity against some of the most aggressive and fatal carcinomas, such as advanced testicular cancer. In 1971, NCI began clinical trials with this compound, called cisplatin. Results were so promising that after a year, testing began in humans.

At first, cisplatin caused such high renal toxicity and severe nausea that researchers felt it would be impractical to pursue as a therapeutic agent. Eventually, however, they found that the kidney toxicity could be eliminated by giving large amounts of water and diuretics; they were also able to reduce the nausea.

Persistence was rewarded by cisplatin's dramatic anti-cancer effects. Today, it is the most widely used drug in chemotherapy for solid tumors. These cancers, which affect body organs, had been especially resistant to treatment.

Although cancer of the testis accounts for only about one percent of all cancers in males, it is still the most common cancer in men between 20 and 34 years of age. Only 10 years ago testicular cancer was often fatal because of its rapid spread to the lungs and other vital organs. But in recent years it has become one of the most curable of cancers, especially if found at an early stage. The improved outlook now for patients with testicular cancer is chiefly due to more effective anticancer drugs, notably cisplatin, as well as to better diagnostic tools.

Barnett Rosenberg, Ph.D., was awarded the Kettering Prize for his discovery of cisplatin, a cancer chemotherapeutic agent that has saved many lives. NIH PHOTO 1968

Cisplatin is also one of the most useful drugs used to treat advanced ovarian cancer. Used in combination with other drugs, cisplatin significantly increases the percentage of patients who respond to treatment.

Cisplatin has also been very effective against bladder cancer, a tumor that 38,000 people in this country alone develop each year, and one that often recurs. In conjunction with surgery and radiation, the drug also helps prevent recurrences.

In addition to its use against these three types of tumors, cisplatin is also being tested against many others. Dr. Rosenberg is researching other platinum compounds, hoping to find one that might be more effective and less toxic than cisplatin.

According to NCI Director, Dr. Vincent DeVita, cisplatin is a "revolutionary drug," and Dr. Rosenberg's work as a physicist is a fine example of the importance of a variety of disciplines working together in the fight against cancer.

Dr. Rosenberg did not become involved in cancer research until his chance discovery. But Dr. Robert C. Gallo, winner of the 1984 Charles Mott Award for his outstanding contribution to understanding the causes and prevention of cancer, has devoted his career to cancer research. He is Chief of the NCI Laboratory of Tumor Cell Biology.

Dr. Gallo was awarded the Mott Prize for his discovery of Human T-cell Leukemia Virus-I (HTLV-I) as a cause of adult T-cell leukemia. In this form of cancer, the body's T-cells, white blood cells that normally stimulate the immune system to fight disease, grow uncontrollably. Short survival is characteristic.

Adult T-cell leukemia is most prevalent in southwestern Japan, but is also endemic to the Caribbean, South America, Israel, Africa, and the southeastern U.S. Some scientists speculate that the virus may have come to the Americas with the African slave trade.

HTLV-I, the first virus now known to cause cancer in humans, is a retrovirus. Retroviruses are members of a family of

**Robert C. Gallo, M.D., won the Mott Prize for finding Human T-cell Leukemia Virus—the first retrovirus known to cause cancer in humans.** NIH PHOTO 1969

viruses that transcribe their genetic information from RNA to DNA and integrate into the DNA of infected cells.

A key step came in 1976 when Dr. Gallo identified a growth factor, now known as Interleukin-2, that promotes the growth of T-cells, thereby making it possible for scientists to study them in the laboratory. Using this growth factor and other techniques of molecular biology, Dr. Gallo was able to show that this retrovirus is a cause of adult human T-cell leukemia.

The evidence that HTLV-I causes adult T-cell leukemia is clear, from animal, epidemiological, and biological studies that show it transforms fresh human T-cells, taken directly from bone marrow, blood, and umbilical cord blood, into cells resembling leukemic cells.

HTLV-I is one of three subgroups of human T-cell leukemia-lymphoma viruses that Dr. Gallo has found and characterized. There are now more than one hundred isolates of HTLV-I. HTLV-II virus has also been isolated in patients with certain types of lymphomas.

HTLV-III, another subgroup of the HTLV retroviruses, has been found by Dr. Gallo to be the probable cause of Acquired Immune Deficiency Syndrome (AIDS). He has observed that HTLV-I and HTLV-III cause diseases that have opposite manifestations—HTLV-I causes T-cells to proliferate, resulting in leukemia; HTLV-III kills T-cells, causing the immunosuppression that is characteristic of AIDS.

Dr. Gallo and his colleagues at NCI have now developed a test to detect the virus in donated blood before the blood is used for transfusion. Licenses were recently granted to several drug companies for further development and distribution of test kits for this purpose.

Dr. Gallo's work has had a considerable impact on cancer research. It confirms the theory that some cancers are caused by viruses and thereby opens the way to developing more effective means for the treatment, cure, and ultimately prevention, of cancer.

Studies of viruses have also played a vital role in the work of Drs. Harold E. Varmus and J. Michael Bishop, 1984 joint winners of the Alfred P. Sloan Prize, awarded for outstanding contributions in the basic sciences to understanding cancer. The two virologists were honored for their discovery that potential cancer-causing genes in cells are contained among the cell's own normal genes.

The work of Drs. Bishop and Varmus, both of the University of California School of Medicine in San Francisco, began in 1970. During a series of experiments to clarify how retroviruses affect cells, they challenged an idea prevalent at the time that it was viral DNA in the cells that triggered the cancer process. In doing so, they made a discovery that has had a major impact on cancer research.

They began by comparing the genes of Rous sarcoma virus (RSV), known to cause cancer in chickens, with the genes of a Rous-associated virus that could not induce sarcomas in chickens. They then isolated the gene present in the cancer-causing RSV but not found in the associated related virus.

Using this so-called sarcoma or "*src* gene" they were able to show that normal cells contained DNA that matched the DNA in the *src* gene. In other words, *src*-like genes with the potential for causing cancer are a part of the normal cells found in many species. Since they have been so well preserved in evolution, and because the proteins made by them appear to regulate growth and development, scientists feel that these cellular oncogenes may exist to perform normal functions such as differentiation. However, in some circumstances they may produce inappropriate amounts or types of proteins, leading to the uncontrolled cell growth characteristic of cancer.

If this theory proves to be valid, scientists may one day be able biochemically to block these proteins and thereby interrupt the cancer process.

The pioneering work of Drs. Bishop and Varmus, giving fundamental importance to the existence of oncogenes, has profound significance for biological research. It suggests that although cancer is many different diseases, there may be common mechanisms by which they arise.

The studies of Drs. Bishop and Varmus, and those of the other prizewinners, offer hope for the treatment, and ultimate prevention, of cancer. According to Dr. Joseph Fortner, President of the General Motors Cancer Research Foundation: "Hope for better treatment, greater understanding, and ultimately prevention, would not exist today without the major contributions of scientists and physicians around the world." ■

**Drs. J. Michael Bishop (left) and Harold E. Varmus shared the Sloan Prize for their work on oncogenes—potentially cancer-causing genes contained in normal cells.**
NIH PHOTO 1970 NIH PHOTO 1971

# Conference Held on Monoclonal Antibody Advances in Kidney Research

Jim Fordham

"The study of monoclonal antibodies has the potential to revolutionize scientific understanding of the cellular aspects of immune responses of the kidney," said Dr. William Couser of the University of Washington in his introductory remarks as co-chairman of the Conference on Monoclonal Antibodies in Renal Research.

The meeting, sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), was held at NIH on May 3–4. Attended by approximately 140 immunologists, pathologists, cell biologists, renal physiologists, nephrologists and other clinicians, the conference was designed to review the many applications of monoclonal antibody technology in renal research.

Major topics addressed were the use of monoclonal antibodies (pure antibodies made in the laboratory from hybrid cells) to further define structural elements of the kidney, to better define the functional aspects of the kidney, and to characterize components of the immune system leading to kidney disease. Other important discussions centered on new developments in the biotechnology of antibody production, including new prospects in the use of molecular genetic techniques.

Monoclonal antibodies also have a major role in the immune monitoring of kidney transplant patients. Dr. Marvin Garovoy, Director of the Immunogenetics and Transplantation Laboratory of the University of California Medical Center at San Francisco, described techniques used by scientists to monitor the immunity of kidney transplant patients and to estimate their relative risk of experiencing a rejection episode. Dr. Garovoy said that studies reported since 1981 have shown that patients with normal to high ratios of helper/cytotoxic-suppressor cells are at increased risk of rejection episodes while patients with low ratios experience lower incidences of rejection.

"It has been shown," Dr. Garovoy reported, "that during the early months post transplant, a stepwise increase in the percent of circulating helper cells can be observed to precede and to predict a rejection episode by as many as five to seven days." If the ratio is low following antithymocyte globulin therapy, he noted, the patient's risk of having a rejection episode within the next two weeks is considered to be very low.

Dr. Garovoy said that although these early results are encouraging, approximately 50 percent of patients do not show the marked shifts in the proportions of helper or cytotoxic/suppressor cells, indicating that the changes in ratio do not occur in all patients.

Dr. Robert Kirkman, Assistant Professor of Surgery at Harvard Medical School and Brigham and Women's Hospital in Boston, reported results of an NIADDK-supported clinical trial in 19 patients in which the monoclonal mouse antibody Anti-T12 was used successfully to treat acute renal rejection. Dr. Kirkman said that the study results "show that one can reverse the rejection episodes and clear the cells of infiltrate with Anti-T12 therapy." He said that except for low-grade fever, complications of treatment were rare.

Dr. Gideon Goldstein of the Ortho Pharmaceutical Corporation reported on a multi-center randomized study comparing the efficacy and safety of therapy using the murine antibody Orthoclone OKT3 with conventional steroid treatment of acute renal rejection. He said OKT3 was found to be safe and significantly more effective than conventional therapy in reversing early rejection episodes.

"Following successful reversal of rejection," Dr. Goldstein said, "patients in both groups were treated conventionally and there were similar incidences of rerejection and kidney loss." He said that the overall success in preserving graft function, without the use of high dose steroids, was due to the initial high reversal rate. Adverse reactions, according to Dr. Goldstein, included fever, chills, chest tightness, wheezing, nausea and vomiting. These occurred only briefly following initial doses and not thereafter. "OKT3 therapy," said Dr. Goldstein, "is highly effective with no long-term adverse effects." Unfortunately, results to date do not support superior efficacy of OKT3 compared to conventional therapy in long-term graft survival.

Another NIADDK-supported scientist, Dr. Paul Terasaki, Professor of Surgery at the University of California Medical Center in Los Angeles, reported studies in which rejection episodes were reversed in 17 patients using two different monoclonal antibodies known as CBL-1 and CHAL-1. He said that an important characteristic of these antibodies is that they are directed against the most highly activated lymphocytes (the cells apparently mediating transplant rejection).

Dr. Terasaki indicated that studies of these antibodies so far are not completely successful, and he pointed to the possibility of future experiments in which CBL-1 and CHAL-1 are used in combination with each other or with additional antibodies.

Dr. Gary Striker of the University of Washington discussed the characterization of glomerular cells by monoclonal antibodies. Dr. Striker described the work of his group in identifying glomerular cells in culture according to morphology, markers, and biosynthetic capabilities. He outlined techniques of identifying, isolating and studying various types of glomerular cells in culture. He also presented the results of experiments in which glomerular endothelial cells were isolated, propagated, and cloned.

NIADDK-supported scientist Dr. Helmut Rennke, Associate Professor of Pathology at Harvard Medical School and Brigham and Women's Hospital in Boston, presented the results of morphologic studies using a special fluorescence technique with monoclonal antibodies to characterize renal antigens.

An overview of immune regulation was presented by Dr. Edgar Engelman of Stanford University School of Medicine. He discussed studies of the functions of B cells (that secrete antibodies), T cells (that help or suppress cell activity), and killer cells (that destroy other cells). He described the use of surface markers to distinguish these cells, and techniques used to separate cells with suppressor capability from those with a cytotoxic function. Dr. Engelman said that he and his colleagues are applying these and other techniques to the study of the immunity of AIDS patients in the Stanford and San Francisco Bay areas.

Dr. Timothy Springer, Associate Professor of Pathology at Harvard Medical School and the Dana-Farber Cancer Institute in Boston, discussed use of monoclonal antibodies as probes of the functions and biochemistry of cell surfaces. Focusing on genetic deficiencies and the molecular bases of disease, Dr. Springer emphasized the importance of monoclonal antibodies in identifying cell surface molecules and in the guidance of gene cloning.

Among other topics discussed at the conference, were monoclonal antibodies in defining transplantation antigens, overview of characterization of renal antigens using monoclonal antibodies, and monoclonal antibodies in induction of experimental kidney disease. ■

# MEDICAL CAPSULES

Sandra D. Levine

- Diabetics exhibit an abrupt increase in blood glucose levels and/or insulin requirements between 5 and 9 in the morning, even before the first meal.

This so-called "dawn phenomenon" had previously been identified in patients with insulin-dependent diabetes mellitus (IDDM), but now has also been demonstrated in noninsulin-dependent diabetics.

A recent study at the Mayo Clinic, funded by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), assessed 20 patients with IDDM and 13 patients with noninsulin-dependent diabetes mellitus (NIDDM) during overnight feedback-controlled intravenous insulin infusion.

There was a comparable significant increase in plasma glucose concentrations present in both groups between 5:30 a.m. and 9:00 a.m. Insulin requirements increased by more than 50 percent, and this increase was sustained for at least an hour and a half between 6:00 a.m. and 9:00 a.m. in 77 percent of the noninsulin-dependent patients (10 of 13) and in 75 percent of the insulin-dependent patients (15 of 20).

The study indicates, therefore, that the dawn phenomenon occurs with almost equal frequency in patients with noninsulin-dependent diabetes as it does in insulin-dependent diabetics. The variability of this phenomenon, however, must be taken into account in adjusting nighttime insulin doses.

Results of this study were reported in the March 22 issue of the *New England Journal of Medicine*.

- The incidence (number of newly diagnosed cases) and death rates of invasive cervical cancer have declined significantly over the past 25 years, according to a study by the National Cancer Institute (NCI). This decline can probably be attributed in part to progress in screening, early diagnosis, and treatment of cervical cancer in its preinvasive stage.

Results of the study, reported in the May issue of *Obstetrics and Gynecology*, indicate that the rates of invasive cervical cancer were higher among black women and among women of low socioeconomic status.

Overall, however, both incidence and mortality decreased by 50 percent from the 1950s to the 1970s.

- Even individuals with lactose intolerance may be able to eat yogurt, according to a recent study.

Many adults who are not of northern European origin are deficient in lactase, the enzyme that breaks down lactose, the major sugar in dairy products. This lactase deficiency causes abdominal pain, gas, or diarrhea when products containing lactose are consumed.

Researchers at the University of Minnesota, under a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), tested 10 lactose-intolerant subjects. Using breath hydrogen measurements to assess lactose absorption, the subjects were tested in the fasting state and hourly for eight hours after eating the following test meals: lactulose (a nonabsorbable disaccharide); lactose; milk; and yogurt.

Ingestion of the yogurt produced only one third the amount of breath hydrogen excretion than was produced by the other test meals, indicating much better lactose absorption.

The symptoms reported by the subjects following ingestion of the test meals also support the finding that the lactose in yogurt was better absorbed. Eighty percent of the subjects reported diarrhea or gas after ingesting the milk; only 20 percent had these symptoms following the yogurt meal.

The researchers believe that the improved absorption of lactose from yogurt may result because the organisms in the yogurt themselves produce enough lactase to aid ingestion.

According to the researchers, this autodigesting feature of yogurt is significant because yogurt may now be considered a well-tolerated source of milk by people with lactase deficiency.

- Each year 150 thousand Americans, mainly young adults, suffer a respiratory disease that strikes without warning and can cause death. Adult respiratory distress syndrome (ARDS) as the disease is called is most often triggered by a nonrespiratory ailment or injury. It occurs when the capillaries in the lungs develop breaks, allowing fluid to leak into the air sacs. For 60 percent of those afflicted, ARDS proves fatal.

Scientists at Vanderbilt University Medical Center in Nashville, supported by the National Heart, Lung, and Blood Institute (NHLBI), have been conducting research ranging from basic cell biology to clinical drug trials to find a cause and treatment for ARDS. So far, no effective treatment has been found to counteract the diffuse injury to the lungs characteristic of this syndrome. It appears that when bacteria produce endotoxins that irritate the lung tissue, the granulocytes (infection-fighting white blood cells) not only destroy the bacteria, but also attack the cells lining the capillary walls.

Now, the Vanderbilt researchers, headed by Dr. Kenneth Brigham, have developed a radioisotope technique that can detect damage to the cells in the lungs aiding physicians in halting the condition before it becomes critical.

The technique measures the soundness of the capillaries by injecting radioisotopes into the blood as it enters the lungs, and comparing the isotope concentration with the concentration in the blood as it leaves the lungs. If the amount decreases, isotope may be escaping through holes in the capillary walls.

Studies are also underway to find effective drug treatments for ARDS. The most promising appears to be methylprednisolone, which inhibits synthesis of the toxins that destroy the capillary walls. The two-year study is the first large-scale drug trial for ARDS.

The researchers hope that eventually, with new techniques of detection and treatment, chances of survival will greatly increase for victims of this disease.

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